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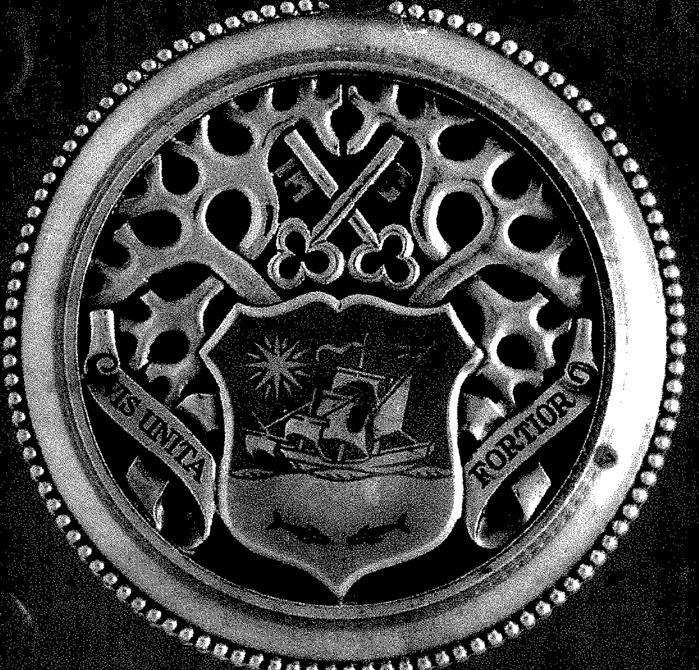

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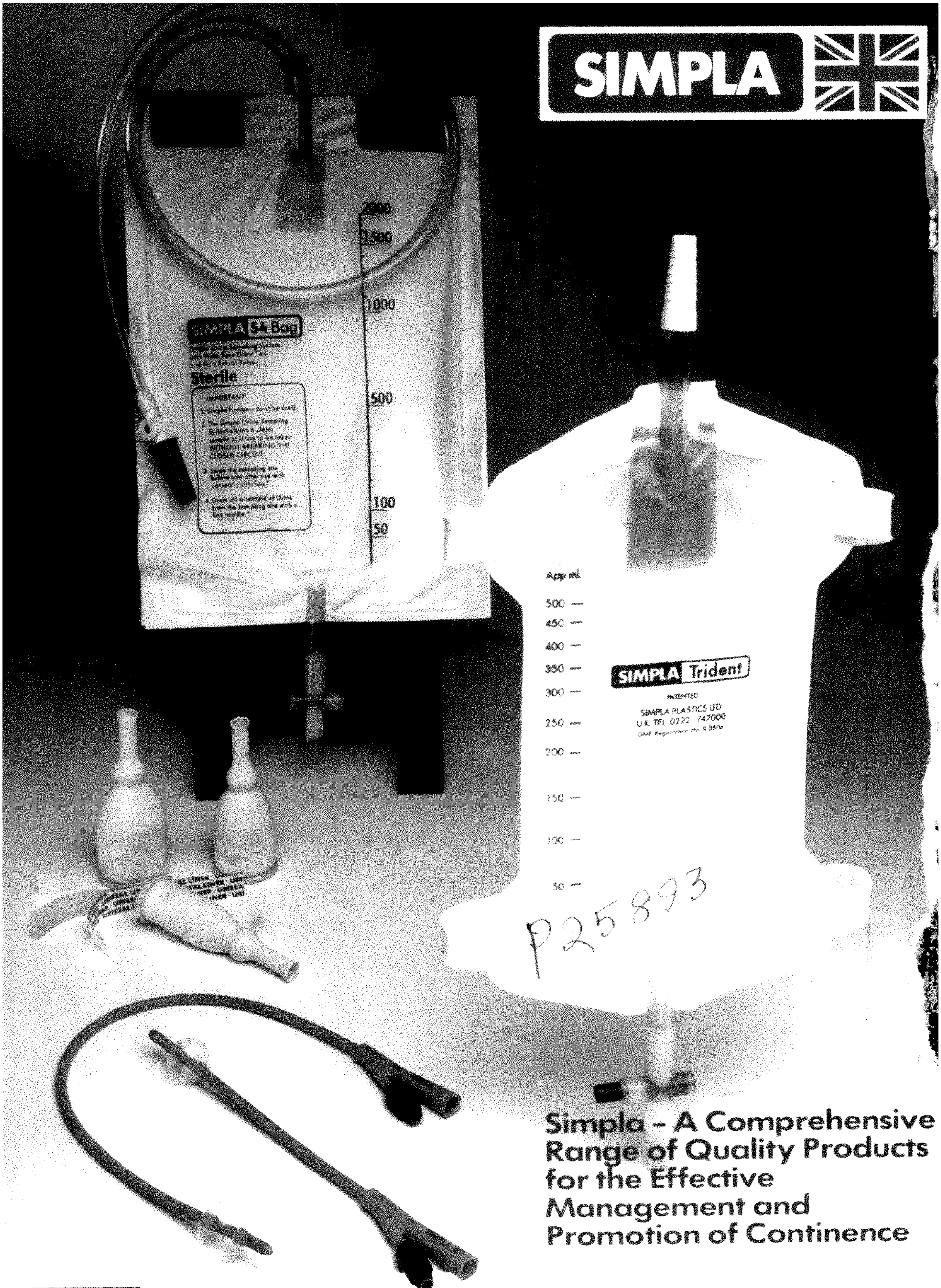

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REVIEW

Late Malignancy Risk in Urology

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The long-term survival of children with congenital urological abnormalities is now taken for granted. In general, they have been found to grow up well after many operations and often in the face of considerable handicaps. Their survival carries with it numerous complications, the most frightening of which is the development of cancer. Successful treatment of congenital abnormalities does not excuse the patient from developing cancers to which the general population is prone, but some conditions and some treatments raise specific risks.

Urinary Diversion

Ureterosigmoidostomy

The most important change that occurs in ureterosigmoidostomies is neoplastic. The first case of carcinoma of a ureterosigmoidostomy was reported in 1929, but only 18 cases were reported up to 1970. Presumably few patients with ureterosigmoidostomy lived long enough to develop the tumours.

Aetiology and research background

The tumour arises at the anastomosis or very close to it in 90% of cases. In patients diverted for benign disease 95% are adenomatous (adenomas or adenocarcinomas), but 2 transitional cell carcinomas and 1 lymphoma have been reported. The most important aetiological factor, both experimentally and clinically, is the mixture of urine and faeces at the anastomotic site. Urine can be found throughout the colon but tumours do not occur as a result.

The increased risk of carcinoma in patients with ureterosigmoidostomy has been variously estimated at 100 to 7000 times that in the normal population (Stewart *et al.*, 1982). Stewart accepts the lower figure.

Estimates of risk have been plagued by the lack of a uniform population at low risk of other neoplasms. This problem was solved by looking at the incidence of colonic cancer in 42 adult exstrophy patients in whom, at some time, urine and faeces had been mixed, compared with 61 patients who had never had such a diversion. There were 4 cancers and 4 non-invasive neoplasms at the ureterosigmoidostomy. No cancers occurred in the non-ureterosigmoidostomy group. The risk was 1726 times the expected incidence. In these "at risk" patients the incidence of neoplasia is 19% and still rising (Strachan and Woodhouse, 1991).

Very few ureterosigmoidostomies are performed nowadays. However, there is growing enthusiasm for lower urinary tract reconstruction using segments of bowel. As there is concern that the same malignancies may arise, it is worth outlining the theoretical background to ureterosigmoid carcinoma.

In rats, union of the urinary and faecal streams is as potent a carcinogen as dimethylhydrazine (DMH) or N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT), which are themselves very potent urinary and bowel carcinogens respectively. Union of the urinary tract with the colon, but with the faecal stream excluded, does not precipitate tumours (Crissey *et al.*, 1980; Strachan *et al.*, 1987a).

In humans, the same applies: neoplasms occur when the 2 streams are mixed. They are very rare in isolated conduits, where only 6 carcinomas have been reported (3 in colonic and 3 in ileal conduits). No neoplasms have been found in 37 years of

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follow-up of the Boyce–Vest diversion (Kroovand and Boyce, 1988).

The presence of urine within the intact sigmoid colon does not cause major histological changes on conventional examination. On haematoxylin and eosin staining of biopsies, normal colonic epithelium is seen abutting normal transitional cell epithelium with inflammatory cell infiltrate. The orifice may become sufficiently prominent and inflamed to earn the title of inflammatory polyp. Even in long-standing anastomoses the junction between the 2 epithelial types is abrupt.

Histochemistry, however, does show differences from normal. For example, staining with high iron diamine alcian blue identifies areas of sialomucin production. Sialomucins are produced by cells in the bottom of normal colonic crypts. Production by other cells is a pre-malignant condition at least in some circumstances: it is seen as an intermediate change when carcinomas are induced in the rat colon and in areas adjacent to human colonic carcinomas, where it is called transitional mucosa (Filipe and Branfoot, 1976). Positive sialomucin staining has been found through the full depth of the crypts in colonic biopsies in 17 of 19 patients with ureterosigmoidostomies. The appearances were the same even when the urine had been through the colon for only a short time before conversion to a different diversion (Silverman *et al.*, 1986). In a patient with adenocarcinoma of the ureterosigmoid anastomosis, positive sialomucin staining was found in all areas of the colectomy specimen (Strachan *et al.*, 1987b).

Colonic cellular activity is also increased both in the presence of urine alone and, more so, with urine and faeces. Strachan *et al.* (1987b) found increased crypt cell production rates and cellular diploid DNA in rats.

The significance of this type of change is unknown. It could be an innocent change in colonic mucosa caused by the presence of urine or it could indicate that urine produces, almost invariably, a pre-malignant change of long latency. It is not seen in colonic conduits.

These clinical and experimental observations do not explain the cause of the tumours. Because they are adenomas and adenocarcinomas and because adenomatous metaplasia has not been reported in ureteric biopsies at colonoscopy, it has been assumed that they arise from the colon. Research has, perhaps, been biased in this direction. It is equally possible that the tumours arise from the ureter (that is the anatomical site at which they are found). In the author's patients, biopsies from the ureteric orifice have almost always shown inflammation and, in 1 case, dysplasia. In 5 cases the transitional cell mucosa formed an inflammatory polyp.

Experimentally, no neoplasms are seen when a length of ileum is interposed between the urothelium and the colon (Gittes, 1986). On the other hand, when a free graft of transitional urothelium is made to colon in a rat, the same neoplasms are seen at the graft edge but they are smaller and more delayed than with a ureterosigmoidostomy (Strachan *et al.*, 1987a).

The carcinogenic agent may be an N-nitroso compound. These potent carcinogens are present in ureterosigmoid effluent in a concentration 10 times greater than in normal bladder urine. The concentrations found in isolated ileal and colonic conduits are variable between patients and in individual patients at different times of day: the only reasonably consistent finding is low concentrations when the diverted urine is sterile.

The relevant compounds are amines. They may be produced by the action of bacteria on urinary nitrates and faecal secondary amines (Stewart, 1986). Whether any combination of mixed bacteria can do this is uncertain, although some research has suggested this to be the case (Stewart, 1986; Kalble *et al.*, 1990). A consistently high carriage rate of *Peptostreptococcus* species has been found in ureterosigmoid effluent in the author's patients (Silverman *et al.*, 1986). This interesting organism is a powerful ureolytic agent (the first step in producing nitrates from urea) and is also capable of performing many of the major biotransformations of bile which have been implicated in the formation of procarcinogens and tumour promoters involved in the pathogenesis of bowel carcinomas.

Presentation

Symptoms from adenocarcinoma of a ureterosigmoidostomy occur late in the disease. Half of the patients have rectal bleeding and about a quarter each abdominal pain or constipation (Stewart, 1986). Some patients with no bowel symptoms have been found to have ureteric obstruction which may or may not have been painless.

Now that this condition has been found to be so common, all cases should be found early during colonoscopy. Any "lump" at the ureteric orifice should be regarded with suspicion and biopsied. The author has found a tumour 6 mm in diameter which was a moderately differentiated adenocarcinoma with invasion. In other words, such tumours do not behave as primary colonic neoplasms where a tumour less than 1 cm in diameter would not be malignant.

The predisposing factor to neoplasia is that there has *ever* been an anastomosis between the urinary and faecal streams. Thus the anastomosis is at risk in patients whose diversion was changed to an ileal conduit, leaving the original anastomosis between ureters and colon *in situ*. Another small group who are at risk will have had a ureterosigmoidostomy converted to a colonic conduit, maintaining the original ureterocolic anastomosis.

The shortest period of exposure to risk (*i.e.* the period with a ureterosigmoidostomy before conversion to an ileal conduit) is 9 months (Spence *et al.*, 1979). The mean time from exposure to development of the tumour is 18 years for benign tumours and 25 years for malignant tumours. The mean age at presentation is 35 years (Stewart, 1986).

Bearing these figures in mind, it would be prudent to begin annual colonoscopies on the tenth anniversary of the ureterosigmoid diversion and to continue indefinitely.

A surgeon who is converting a ureterosigmoidostomy to any other diversion should make a point of resecting the original anastomosis. Similarly, if a laparotomy is required in a patient with the original anastomosis still intact, the opportunity should be taken to resect it.

Treatment

Patients presenting with symptoms usually have extensive local disease and many have metastases. There is a high early death rate whatever is done (Spence *et al.*, 1979).

When the condition is found at colonoscopy, the tumour should be small, localised and often benign. The author's practice is to excise the lower 2 cm of ureter and an adjacent cuff of colon, and also resect the other lower ureter and a smaller cuff of colon, though in 6 specimens only inflammation has been found.

Diversion after this resection may be of the continent internal type. However, many patients opt for a further ureterosigmoidostomy. This practice has an honourable tradition, being the choice in 50% of the collected cases reviewed by Spence *et al.* (1979). Only one case of recurrence at the new anastomotic site has been reported.

Continent Internal Diversions

It is the constant fear of surgeons who perform these operations on the young that history will repeat itself: the bowel segments will develop neoplasia in the same way that the ureterosigmoidostomy did. If the faecal and urinary streams must be mixed for neoplasia to occur, the risk may be small. However, if it is chronic mixed bacterial infection, rather than the faeces *per se*, that is required, the risk may be high.

In patients with colonic and ileal cystoplasties, high levels of nitrosamines were found in the urine of a group of 23 patients. Biopsies of the ileal and colonic segments showed changes similar to those that have been found in ileal and colonic conduits and in ureterosigmoidostomies. More severe histological changes and higher levels of nitrosamines correlated with heavy mixed bacterial growth on urine culture (Nurse and Mundy, 1989). The inflammatory changes seen in these pouches and in conduits are probably innocent.

Fourteen cases of pouch neoplasms have been reported. In some cases the neoplasm occurred so soon after the reservoir construction and in elderly patients that a pre-existing lesion seems probable. Others are more worrying, particularly as the problem seems commoner in patients with ileocystoplasty. The mean time to tumour development is 18 years (Filmer and Spencer, 1990).

Undescended Testes

Bilateral

There is no doubt that cryptorchidism predisposes to germ cell neoplasia. The question is, to what extent?

The classic review of 13,089 cases of germ cell tumour from the literature by Whitaker (1970) gave a 9.8% incidence of undescended testes (UDT) or a 35-fold increase in risk. The number of patients with bilateral UDT is not recorded. The risk of neoplasia, if these figures are accepted, depends on the incidence of UDT in the population. Although the best figures available at the time, Whitaker (1988) has cast some doubt on them recently.

In calculating an accurate figure, the statistician has to allow for the changing incidence of both the neoplasm and UDT. The incidence of testicular neoplasms is increasing in some countries, especially Denmark, and remains rare in negroes. The risk may differ by time and place.

Denmark has a particularly good cancer and population registry. In 167 men with bilateral UDT seen between 1949 and 1960 there were 4 cases of neoplasia (3 seminoma and 1 embryonal carcinoma). The risk was 9.3-fold over the normal population. The number of seminomas produced a late age of diagnosis, so that the high risk period was in the fourth decade of life (Giwercman *et al.*, 1987).

Chilvers and Pike (1989) have calculated from the world literature that the overall increased risk of neoplasia in patients with any UDT is 5.4. At the Royal Marsden Hospital they calculated the relative risk at 5.1. The relative risk for those with bilateral UDT was 11.7, which compares well with the Danish figure. Approximately 1 boy in 44 with bilateral UDT will develop a neoplasm (Chilvers and Pike, 1989).

The higher the testes in the abdomen, the greater the risk of neoplasia. Some intra-abdominal testes do not contain any germ cells and so, presumably, cannot develop a germ cell neoplasm. However, the underlying trend has been confirmed by the incidence of carcinoma *in situ* (CIS) in undescended testes at various levels in adults. CIS was found in 4 of 16 intra-abdominal testes compared with 3 of 44 inguinal testes (7%). Ten of the 16 abdominal testes contained Sertoli cells only (Ford *et al.*, 1985).

Carcinoma *in situ* can be found in biopsies of the pre-pubertal testis taken at orchiopexy. An incidence of 7 cases in 1331 biopsies has been reported (Hadziselimovic *et al.*, 1984). The significance of *in situ* change at this age is unknown.

Unilateral

Calculation of the risk of neoplasia in unilateral UDT is subject to the same difficulties and variations as in bilateral UDT.

The Danish study showed that the increased risk for unilateral UDT was only 2.4 (Giwercman *et al.*, 1987). For Englishmen the relative risks have been given as 4.0 for the undescended testis and 1.7 for the scrotal testis; the overall risk was 6.8, which is about half the risk for those with bilateral UDT. About 1 boy in 120 with unilateral UDT will develop a neoplasm (Chilvers and Pike, 1989).

Carcinoma *in situ* is uncommon in the normally descended testis. There were no cases in 400 autopsies of men aged 18 to 50 years after sudden death (Giwercman *et al.*, 1988). It was found only once in a series of 30 biopsies of the normal testis in unilateral UDT and was never found in 52 cases of successful unilateral orchiopexy (Ford *et al.*, 1985). Skakkebaek's group found CIS in 2% of biopsies of men with a history of UDT, though it is not said which testes were considered; this incidence is higher than in any reports of infertile men (Giwercman *et al.*, 1988).

In practice, successful orchiopexy does not completely abolish the risk of neoplasia. However, there are few reported cases in boys undergoing successful orchiopexy before 10 years of age and none in those undergoing surgery before the age of 6. In unilateral UDT, 20% of cases occur in the normal testis.

Gonadal Neoplasia in Intersex Disorders

One of the most influential factors in the management of patients with intersex is the risk of neoplasia in the gonads. Biopsy may be necessary to define both the type of gonad present and the neoplastic risk. The majority of neoplasms are of germ cell origin and so some germ cells must be present in the gonad, primitive and small in number though they may be. Indeed the risk of neoplasia is higher with more dysplastic germ cells, or with the coexistence of ovarian and testicular tissue in the same gonad (as in true hermaphroditism).

Gonadal dysgenesis

In gonadal dysgenesis the gonads may contain testicular tissue or be a streak, or there may be one of each (Robboy *et al.*, 1982). Both are at risk. The "testis" has a 30% incidence of gonadoblastoma which may become invasive. Dysgerminoma/seminoma may occur in the streak gonad. Non-seminomatous germ cell tumours occur rarely in dysgenetic gonads.

The risk is highest in the group with pure gonadal dysgenesis with 46XY chromosomes. They have a 20 to 30% incidence of gonadoblastoma, of which about one-third will progress to malignancy (Savage and Lowe, 1990).

Neoplasms may occur before puberty, although the risk is said to rise rapidly after puberty. However, in a personal series, Savage and Lowe (1990) reported 2 of 5 cases in childhood and the remainder in the "peripubertal period".

Gonadoblastomas are composed of Sertoli and germ cells with occasional Leydig cells. They may occur at any age from 6 months (and may possibly arise *in utero*), but are most common in the second and third decades. They are the characteristic tumours of the streak and dysgenetic gonads. There is some doubt as to whether gonadoblastoma is a neoplasm in its own right. It never metastasises as a gonadoblastoma and may undergo spontaneous regression. When metastases occur they are only of the germ cell element. It may be that the germ cell portion of the gonadoblastoma develops malignant change and then metastasises rather than the whole lesion being neoplastic from the outset. The endocrine cells may secrete active hormones, especially testosterone (Savage and Lowe, 1990).

Dysgerminoma, on the other hand, is a malignant germ cell neoplasm from the start, though it metastasises late. The term is, of course, normally applied to classical seminomas arising in the ovary. It is used in this context with seminoma when the nature of the gonad is uncertain, or alone when the gonad is ovarian.

True hermaphroditism

Individuals with a Y chromosome have a high risk of gonadal malignancy. The group is small and the percentage risk is unknown. Those with a testis rather than an ovotestis are particularly at risk. Both gonadoblastoma and seminoma have been described (Savage and Lowe, 1990).

A juvenile form of granulosa cell tumour has been described in the ovarian gonads (Zaloudek and Norris, 1982). These tumours probably arise from "ovarian" mesenchyme but contain large follicular structures and may be oestrogen-secreting. Although the cells have many mitoses, only about 10% are malignant. They may recur many years after removal.

Male pseudohermaphrodites

The only group with a significant risk are those with androgen insensitivity, especially in its complete form of testicular feminisation syndrome. Tumours are rare in childhood, though one case of seminoma was included in the series of Savage and Lowe (1990). There seems to be a higher risk in adults and 3 cases were reported in siblings (O'Connell *et al.*, 1973).

Gonadal biopsies in childhood have identified atypical cells which appear to precede the development of carcinoma *in situ* in adulthood (Muller *et al.*, 1984). The abnormal cells have similar electron microscopic features to seminoma cells, though they are easily recognisable with the light microscope. In male phenotypes who are 45XO/46XY these features are considered to be an indication for gonadectomy (Muller *et al.*, 1984; Savage and Lowe, 1990).

Congenital adrenal hyperplasia

True neoplasia is uncommon in congenital adrenal hyperplasia (CAH). This is not just an unimportant "negative observation". If CAH is poorly controlled in males, adrenocortical rests in the testes may develop hyperplasia. This can produce craggy tumour-like growth of the testes. The condition is bilateral but not necessarily synchronous. It is not neoplastic and the "tumours" disappear when the adrenals are properly suppressed with dexamethasone (Cunnah *et al.*, 1989).

Management of the gonads in intersex

It would be wrong to remove all gonads in all intersex patients. The indications for removal are inappropriate gonadal type for the sex of rearing and high risk of malignancy. The risk of malignancy is partly dependent on the diagnosis which may not always be certain.

In their review of the literature, Savage and Lowe (1990) concluded that neoplasms were present on presentation in 15% of children with mixed gonadal dysgenesis, 5% with androgen receptor defect and 1% of true hermaphrodites. As in the normal population, the neoplasms were commoner in undescended gonads and the higher the gonad the higher the risk. However, unlike the normal population, they may occur at any age, even though the risk is greater in young adults.

Several steps are necessary to assess the future risk of neoplasia in any individual. The first and most important is to establish the diagnosis. The highest risk is in patients with gonadal dysgenesis, with lesser risks in true hermaphroditism and testicular feminisation. There is no increased risk in congenital adrenal hyperplasia. Gonadal biopsy may be indicated. The finding of müllerian duct remnants suggests that gonadal dysgenesis may be present.

In all cases the karyotype will have been determined. Apart from contributing to the diagnosis, knowledge of the chromosomes may help in the assessment: in true hermaphrodites the risk of neoplasia is higher when a Y chromosome is present.

The position of the gonads must be established by ultrasound, CT or laparotomy. The risk of malignancy in high gonads is so high that they should be removed. This is especially so as they are unlikely to be able to produce adequate testosterone in adult life (Kofman *et al.*, 1981).

Exstrophy

Up to 1955, 40 carcinomas had been reported in untreated exstrophy bladders, 33 adenocarcinomas, 2 squamous and 5 of unknown origin (McIntosh and Worley, 1955). In 1944 the incidence of carcinoma was calculated to be 4% (Wattenberg *et al.*, 1956).

There have been few reports since that time. The only case the author has encountered was in a 40-year-old with untreated exstrophy. A case was reported in 1979 in a 71-year-old patient who had remained untreated until he was 59 years old, when he had had a diversion leaving the bladder *in situ*.

The glandular area is in the middle of the bladder, so it would be expected that patients treated by early cystectomy and diversion would not be at special risk of adenocarcinoma.

The cancers occurring in the author's 103 adult exstrophy patients (see ureterosigmoid cancer above) have been reviewed. Cancer occurred only in patients who had had urine and faeces mixed at some time ("at risk" group—42 patients). Eight patients developed colonic neoplasms. Two other patients in the "at risk" group were said to have died of adenocarcinoma of the bladder at 28 and 34 years of age, though both had had cystectomies in early childhood. In one case the information came only from the family doctor's record and there was no post mortem. The other had a post mortem and it was said that the ureterocolonic anastomoses were normal, the cancer arising from the bladder remnant (Strachan and Woodhouse, 1991). Although the evidence, especially in the first case, is weak (a slight doubt remains that the ureterosigmoidostomy had something to do with them), this would give an incidence for the 103 patients of 2% in patients who have had a bladder closure.

Whether or not the epithelium returns to normal after successful bladder closure is not known. In the functioning exstrophy bladder the risk of transitional and squamous carcinomas is, presumably, the same as for any normal individual. It might be increased if the bladder was chronically infected or had repeated stones. The augmented bladder might have a risk of carcinoma for the reasons discussed above.

Second Malignancies in Patients Cured of Childhood Cancer

Patients who have been cured of one cancer are at risk of developing another. A cured child has a 10 times greater incidence of malignancy at 20-year follow-up than an age-matched peer (Meadows *et al.*, 1980).

Second malignancies are particularly associated with Wilms' tumour. Patients with bilateral tumours, associated congenital anomalies and the rhabdoid histological variant are at higher risk (Meadows, 1985).

Radiation in childhood is associated with the development of acute myeloid leukaemia and soft tissue and bone sarcomas. For bone sarcomas there is a dose-response relationship, the relative risk being 8 for doses of 10 to 20 Gy and 30 for doses of 50 Gy or more (Meadows, 1985). Osteochondroma and acute leukaemia may occur up to 26 years after treatment for Wilms' tumour (Byrd and Levine, 1984). The effects may be different when the radiation is given to children as opposed to adults. However, it is comforting to note that in a recent review Hoffman *et al.* (1985) concluded that there was no association between pelvic irradiation and subsequent urothelial malignancy.

Amongst the chemotherapeutic agents actinomycin-D and Adriamycin have been particularly implicated. In this instance the effects of radiotherapy and chemotherapy may not be additive: children given radiotherapy and actinomycin have a 7-fold less incidence of second malignancy than those having radiation alone (D'Angio, 1982). Cyclophosphamide is associated with the development of acute non-lymphocytic leukaemia, bone tumours and solid cancers in an irradiation field (Meadows, 1985).

Bilharzia

The clinical manifestations of Bilharzia vary greatly in different groups. In endemic areas the rate of infestation of children is high and increases with age. Radiological changes occur in approximately 25% of children and are commoner and more severe in boys than girls.

An adult who was infested as a child may have been treated early in the disease and before irreversible changes had occurred; there are unlikely to be any long-term consequences.

Untreated patients may live in symbiosis with their ova for many years, especially if they are well nourished and removed from possible reinfestation.

Cancer in the bilharzial bladder (it is very rare in the ureters) has a number of curious features. It occurs 4 times more often in men than women. It is much commoner in some endemic areas (such as Egypt) than in others. It usually presents in an advanced state in adults in their 30s and 40s. Although clinically aggressive, most cases seem histologically of low grade malignancy. About two-thirds are squamous cell carcinomas and adenocarcinomas, with transitional cell carcinomas being seen occasionally. The manifestations of Bilharzia are less in females, probably because oestrogens inhibit copulation in the parasites, which lessens the egg load.

The incidence of secondary urinary infection is closely related to the incidence of carcinoma. It has been shown that in Egypt where the rate of bacterial infection is high, several carcinogens, especially nitrosamines, are found in the urine. The rate of bacterial infection is particularly high in adolescent boys.

The resulting cancers are often inoperable at presentation. They are resistant to radiation therapy and there have been few responses to chemotherapy. Radical cystectomy and diversion offer the best hope of cure (Husain, 1984).

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The Use of Extracorporeal Shock Wave Lithotripsy for Medullary Sponge Kidneys

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Summary—A number of patients with medullary sponge kidney recurrently form and pass stones with the risk of developing an obstructive nephropathy. These patients may benefit from extracorporeal shock wave lithotripsy to the medullary collections, as this appears to reduce the frequency of symptomatic stone passage.

Medullary sponge kidney (MSK) is a relatively common cause of symptomatic stone formation. The condition is a developmental anomaly of the renal medulla characterised by fusiform and cystic dilatation of the collecting tubules confined to the renal pyramids. It may be restricted to a few pyramids or be diffuse, unilateral or bilateral (Harrison and Rose, 1979). The true prevalence of the condition is unknown as patients may be entirely asymptomatic, the diagnosis being made at intravenous urography performed for some other purpose. When present, symptoms are related to the associated nephrolithiasis. Calcium oxalate or phosphate stones form in the dilated ducts and cysts and erosion of these stones into the collecting system leads to the problems related to their presence and passage.

Treatment of patients with symptomatic MSK has previously consisted of the control of associated metabolic disorders such as hypercalciuria, the eradication of infection and the surgical management of problematic stones and damaged kidneys. The aim of this study was to evaluate the potential role of extracorporeal shock wave lithotripsy (ESWL) in the management of these patients.

Patients and Methods

A total of 22 kidneys in 17 patients were diagnosed as having MSK on the characteristic radiological findings after intravenous urography. These patients were all symptomatic with loin pain and/or recurrent passage of stones. The patients had a mean age at the time of treatment of 48 years (range 34–63). The average duration of symptoms was 12 years, with the majority of patients previously receiving treatment with antibiotics, dietary control and surgical removal of obstructing calculi. Two patients had lost the function of one kidney as a result of stones. Treatment was performed initially on a Wolf 2200 (3 patients) and subsequently on a Dornier MPL 9000 (14 patients), which has both X-ray and ultrasound imaging modalities. The patients were assessed radiologically prior to treatment with intravenous urography, and with plain X-ray 2 weeks and 2 months after treatment. They were subsequently reviewed as out-patients. Urine was cultured and renal function and blood pressure were measured at each visit. Patients were also asked about the symptoms of renal colic, the frequency of stone passage and the incidence of urinary infection both before and after treatment. Two patients required the passage of a double pigtail stent prior to treatment because of the presence of obstructing stones.

Each kidney received a mean of 1.8 treatments, with an average of 1600 shocks at each session.

Based on a Poster Demonstration at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

Treatment was aimed initially at any stones within the collecting system and then at collections of stones within the renal pyramids.

Results

All treatments were well tolerated. Nineteen treatments were followed by the visible passage of stone gravel and haematuria and 17 kidneys showed a reduction in the stone burden of the renal medulla, as judged radiologically 2 months after the final treatment. Radiological reduction in stone burden was described as *good* (>50% reduction in visible stone) (Fig.), *moderate* (0–50% reduction) and *no response* (Table). Urine cultures failed to reveal infection either before or after treatment. Urea, creatinine and electrolytes also failed to show any change. One patient developed significant hypertension 2 months after treatment, though this patient had a contralateral non-functioning kidney which was subsequently removed.

Follow-up continued for a mean of 16 months. Seven patients noticed a long-term reduction in the frequency of passage of stone particles. These were the patients who had been troubled by recurrent passage of gravel, from stones eroding into the collecting system. Renograms were performed in 3 patients before and 7 days after treatment and no deterioration in renal function was detected.

Table Radiological Response of MSK Kidneys to Treatment with ESWL in Terms of Stone Burden

Response	*No.*
None	5
Moderate	11
Good	6

Discussion

Although the incidence of MSK in unselected patients undergoing urography is only 0.5% (Myall, 1970), the incidence among patients presenting with stones has been reported to be as high as 21% (Yendt *et al.*, 1981). The condition is congenital, although there is no evidence of a raised familial incidence. Individuals may be entirely asymptomatic and these benign cases are not associated with any loss of renal excretory function. It can, however, lead to the recurrent passage of stones, which increases the likelihood of an obstructive nephropathy. Several factors contribute to the nephrolithiasis and include urinary stasis within the dilated ducts, defective urinary acidification and hypercalciuria. A raised urinary pH has been reported in up to 40% of patients with MSK (Higashihara *et al.*, 1984) and this is known to facilitate precipitation of calcium phosphate. Hy-

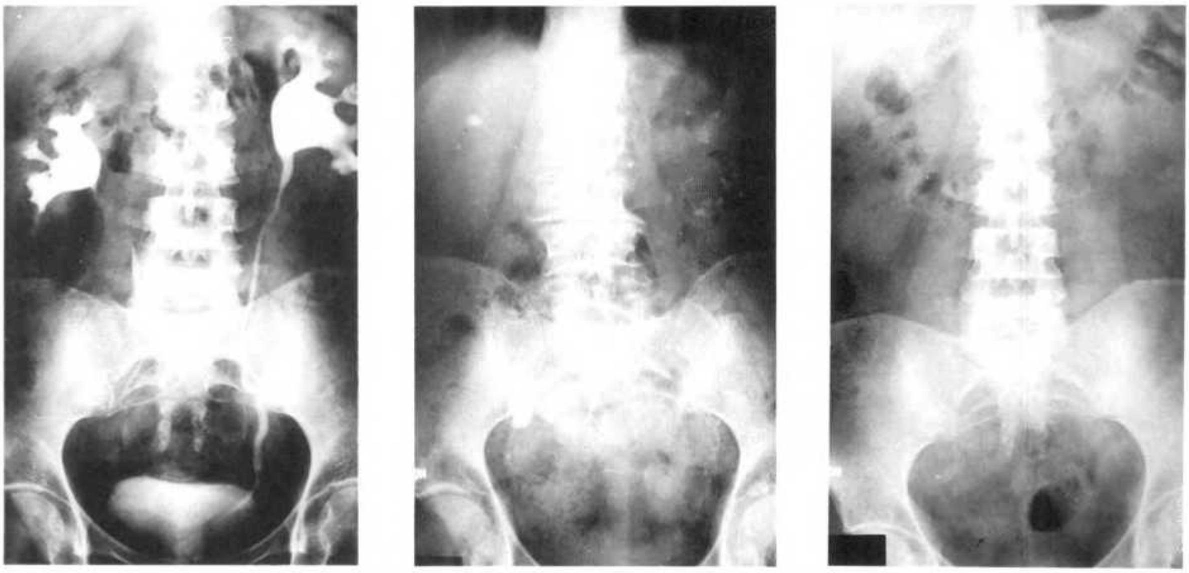

Fig. Radiographs of patient with MSK. Urogram taken prior to treatment, and plain X-rays taken after 1 and 2 treatments, showing >50% reduction in stone burden.

percalciuria occurs in a similar number of patients (Harrison and Rose, 1979); unlike patients with idiopathic hypercalciuria, however, 95% of whom are men, it occurs with equal incidence in women with MSK. The aetiology of this hypercalciuria is unclear. Infection can also increase the potential for stone formation if urea splitting organisms are involved, and is always difficult to eradicate once established.

Treatment of patients with MSK has centred around limiting these contributions to nephrolithiasis. Higashihara *et al.* (1988) treated hypercalciuric MSK patients with alkali (sodium bicarbonate) and reported a reduction in urinary calcium excretion and the frequency of passage of stones. They concluded that acidosis led to a depression in renal tubular reabsorption of calcium. It has been suggested that the acidification defect is the primary event in the pathological sequence of stone formation in these patients (Osther *et al.*, 1988). Treatment of relapsing infection may be controlled with long-term suppressive antibiotics, though eradication is more difficult. Patients with MSK localisd to one portion of the kidney, with damage to that part resulting from recurrent infection, have been treated by partial nephrectomy. The main role of surgery has been the removal of obstructing stones within the urinary tract.

The advent of ESWL increased the potential for treating stones before they caused obstructive nephropathy. Its use in kidneys affected by MSK has been limited (Nakatsuka *et al.*, 1988). This study suggests that it may have a role in treating calculi that are within the collecting system, reducing the number of calculi that are still within the renal medulla and decreasing the number of episodes of colic. All of the stones were not eradicated but it is believed that those that were close to eroding into the collecting system were susceptible to ESWL, or were knocked out of their cysts or dilated ducts.

ESWL to stones within the collecting duct tubules raises the question of whether damage to the tubules ensues. Tubular enzyme levels in the urine were not measured but this may be necessary in a future study. The finding that one of our patients developed significant hypertension 2 months after treatment was clouded by the fact that he had a contralateral non-functioning kidney. Nevertheless, the potential for tubular damage in these patients may be greater than in patients with conventional collecting system calculi and this should be considered when treating patients until further evidence becomes available.

This study suggests that there is a role for ESWL in the treatment of patients with MSK. Patients who recurrently form and pass stones are in danger of developing an obstructive nephropathy. These patients may benefit from treatment to these stones before they accumulate and grow in the collecting system and ESWL appears to be able to do this and reduce the frequency of stone passage. It may be that patients should be treated at suitable intervals, such as annually or biannually, to prevent accumulation of collecting system stones and to remove stones that are close to eroding into the calices. Patients and clinicians can not expect to clear MSK kidneys of stones, but a reduction in symptomatic passage and prophylaxis against obstructive nephropathy are realistic goals.

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In vitro Inhibition of Struvite Crystal Growth by Acetohydroxamic Acid

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Summary—Struvite ($MgNH_4PO_46H_2O$) crystals were produced by *Proteus mirabilis* growth in artificial urine, in the presence and absence of the urease inhibitor, acetohydroxamic acid (AHA). In the absence of AHA, struvite crystals assumed an "X-shaped" or dendritic crystal habit due to rapid growth along their 100 axis. When AHA was present, crystal growth, as monitored by phase contrast light microscopy, was greatly slowed, and the crystals assumed an octahedral crystal habit. Scanning electron microscopy revealed that crystals grown in the presence of AHA were pitted on their surface. This pitting was absent in control samples. While most of this inhibition by AHA was due to lowered urease activity, some crystal growth inhibition occurred in struvite produced in the absence of urease activity through NH_4OH titration of artificial urine. We conclude that while AHA is primarily a urease inhibitor, it may also disrupt struvite growth and formation directly through interference with the molecular growth processes on crystal surfaces.

Struvite ($MgNH_4PO_46H_2O$) calculi arise from urinary tract infections (UTI) by urease-producing organisms such as *Proteus mirabilis* (McLean *et al.*, 1988). The urease-catalysed hydrolysis of urea generates ammonia, elevates urine pH, and causes the precipitation of Mg^{2+} as struvite (Griffith *et al.*, 1976; Hedelin *et al.*, 1985; McLean *et al.*, 1988). Struvite *in situ* associates with an organic matrix of host and possibly bacterial origin (McLean *et al.*, 1988) which enables the development and formation of mature struvite calculi and their retention in the urinary tract. Struvite urolithiasis is notorious for its rapid progression, high rate of recurrence, and severe pathological effects on the kidney (Lerner *et al.*, 1989).

The central role of bacterial urease activity in the pathogenesis of this UTI led to the development of a number of urease inhibitors. Acetohydroxamic acid (AHA), an analogue of urea and a competitive inhibitor of urease activity, represents the only inhibitor currently licensed for therapeutic use (Fishbein, 1982; Rosenstein and Hamilton-Miller, 1984; Williams *et al.*, 1984; Rodman *et al.*, 1987; Hess, 1990). It has been quite successful in clinical trials (Williams *et al.*, 1984) but notable side effects of this compound include tremulousness and thrombosis. Animal studies have also shown the possibility of teratogenic and mutagenic side effects (Hess, 1990).

As part of our ongoing research into the pathogenesis of *P. mirabilis* UTI and struvite urolithiasis, we investigated the effects of AHA on struvite crystal development. Apart from its inhibition of urease activity, AHA also had an inhibitory action against struvite crystal growth that was completely independent of its action against urease. These findings suggest that AHA may be doubly effective as a struvite stone inhibitor, in that it interferes with crystal growth as well as blocking urease activity.

Materials and Methods

P. mirabilis 2573, serotype O-6, used in these experiments was originally isolated from a patient

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with struvite urolithiasis and has been deposited with the American Type Culture Collection as strain ATCC 49565 (Beynon *et al.*, in preparation). The experimental protocol used for crystal growth was described in our earlier publications (McLean *et al.*, 1990a and b, 1991). Briefly, it involved growing *P. mirabilis* in a flask containing 800 ml artificial urine (McLean *et al.*, 1990b). Sterile artificial urine was added to the flask from a reservoir at 60 ml/h, and the waste urine removed through a port on the side of the flask. The urine composition was chosen so as to mimic the average 24-h urine composition of human males. The flask volume and rate of addition of fresh urine represented average male bladder capacity and urine production rates.

During most experiments, AHA was present in the artificial urine in both the growth flask and reservoir (4 mg/ml). In other experiments, we investigated whether AHA could interfere with struvite crystal growth once crystallisation conditions had been established. This involved inoculating the artificial urine with *P. mirabilis* and growing the organism in the absence of AHA for 4 h. At this point, sterile AHA was added to the urine in the reservoir (4 mg/ml), and the mixture was gradually introduced into the culture flask (60 ml/h). Control experiments lacked AHA.

Samples were removed at 0, 0.5, 1, 2, 3, 4, 5, 6, 7 and 24 h after inoculation, and analysed for culture viability, urease activity, ammonia (NH_3, NH_4^+, and total ammonia), pH and optical density (McLean *et al.*, 1990a and b). In addition, samples were examined by phase contrast light microscopy and scanning electron microscopy (SEM), using the equipment and protocols described previously (Clapham *et al.*, 1990; McLean *et al.*, 1990b). We also investigated whether AHA had an effect on struvite crystal growth in addition to its urease inhibiting property. This involved growing struvite crystals in sterile artificial urine through titration with 0.25 M NH_4OH added at 60 ml/h. This titration protocol with NH_4OH yielded approximately the same pH increase kinetics as did *P. mirabilis* growth (McLean *et al.*, 1991). All crystals produced during these experiments were analysed by powder X-ray diffraction and compared with published values for struvite (McLean *et al.*, 1990a). This experimental protocol allowed us to observe the effects of AHA on struvite crystal growth and to ascertain whether any alteration was due to an interference with *P. mirabilis* viability or urease activity, a buffering of ammonia concentrations or pH, or a direct effect on crystal growth.

Results

Growth of *P. mirabilis* in artificial urine in the absence of AHA resulted in a rapid increase in pH, bacterial numbers (colony forming units, CFU), and urease activity (Fig. 1). When AHA was present, bacterial viability was not affected, but urease activity and pH increase were greatly diminished (Fig. 1). Similar although delayed effects were seen if AHA was added after 4 h growth (data not shown).

Crystals produced by *P. mirabilis* growth or NH_4OH titration in the absence of AHA demonstrated the typically dendritic or X-shaped morphologies (crystal habits) of rapid growth along the 100 axis (Figs 2A and B) (Abbona and Boistelle, 1979; McLean *et al.*, 1990b). When AHA was present, crystal growth was delayed and the crystals that did develop exhibited a more 3-dimensional tabular crystal habit typical of slow growth (Figs 3A and B) (Abbona and Boistelle, 1979). Crystal growth was also slowed in crystals produced through NH_4OH titration (Fig. 3B). The deleterious effects of AHA on struvite crystal structure were especially evident upon ultrastructural examination by SEM (Fig. 4). Noticeable pitting was observed on struvite crystals produced in the presence of AHA. All crystals produced in this experiment were identified as struvite by X-ray diffraction. No impurities in a concentration greater than 10% were detected by this technique.

Discussion

A number of urease inhibiting compounds such as AHA have been developed for use in clinical, nutritional and agricultural applications (Fishbein, 1982; Rosenstein and Hamilton-Miller, 1984; Gould *et al.*, 1986; Mobley and Hausinger, 1989; Hess, 1990). In the case of struvite urolithiasis, urease inhibition is especially important in that ammonia production and pH elevation due to the activity of this enzyme represent the major virulence factors associated with this UTI (Griffith *et al.*, 1976; Burns and Gauthier, 1984; McLean *et al.*, 1988).

In light of its urease inhibiting properties, we anticipated that the major effect of AHA inhibition of struvite formation would be due to its lowering of urease activity. Although this did occur, we also found that AHA disrupted struvite formation in a manner quite independent of its action against urease (Figs 3B and 4). As stated before, AHA ($CH_3CONHOH$) is a structural analogue of urea

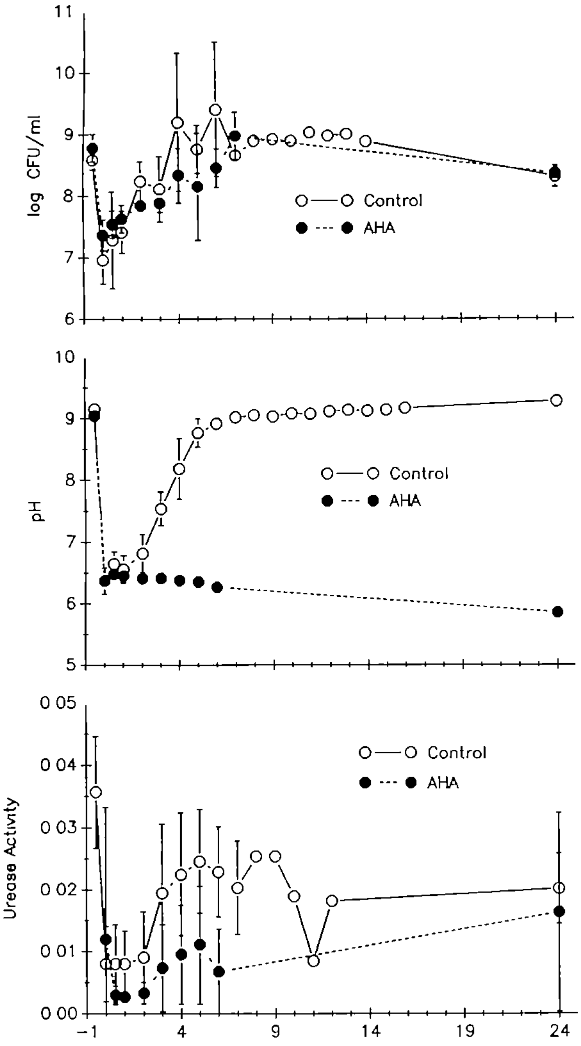

Fig. 1 pH, cell numbers (log CFU/ml) and urease activity due to *P mirabilis* growth in artificial urine in the presence and absence of AHA.

(H_2NCONH_2). From its structure, it is quite conceivable that AHA, by virtue of its -CO (carbonyl) and -NHOH (hydroxamino) moieties, may interfere with struvite formation through hydrogen bonding to the H_2O and PO_4 struvite crystal components or possibly through an ionic complexation of Mg^{2+} to its partially anionic carbonyl moiety. The large quantities of amorphous material and low numbers of crystals present in Fig. 3A suggest that while some precipitation did occur, its molecular re-arrangement into an ordered (crystalline) form was inhibited. Both ionic and hydrogen bonding are involved in struvite crystal development (Abbona and Boistelle, 1979).

AHA is not the only compound that can block struvite growth. Our own work and that of others has shown that naturally occurring urine compounds such as citrate and pyrophosphate are able to inhibit struvite formation through chelating Mg^{2+}, disrupting the hydrogen and ionic bonding of this mineral and coating the surface of struvite crystals, thus preventing further growth (Hedelin *et al.*, 1989; Hugosson *et al.*, 1990a and b; McLean *et al.*, 1990a, 1991).

Although the practical clinical use of AHA is uncertain due to the aforementioned side effects of thrombosis and tremulousness (Hess, 1990), this compound shows a great deal of promise in the control of struvite development by its inhibitory effects against both urease and crystal development. Because of these additional inhibitory effects of the urease inhibitor, AHA, against crystal growth, we would encourage other researchers in the field of developing urease inhibitors to investigate the possibility of their respective test compounds to inhibit struvite crystal growth. The potential clinical implications of developing inhibitors which are doubly effective against both urease and struvite crystal development are very significant.

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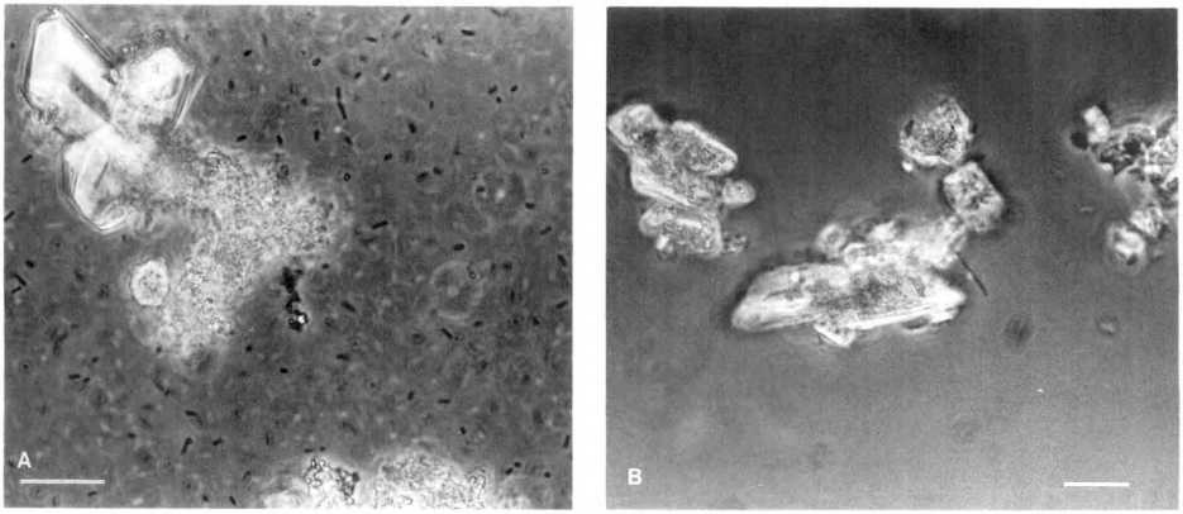

Fig. 2 Crystal habits of struvite formed in artificial urine without added AHA through growth and urease activity of *P. mirabilis* (A) or NH_4OH titration (B). Bar represents 20 μm.

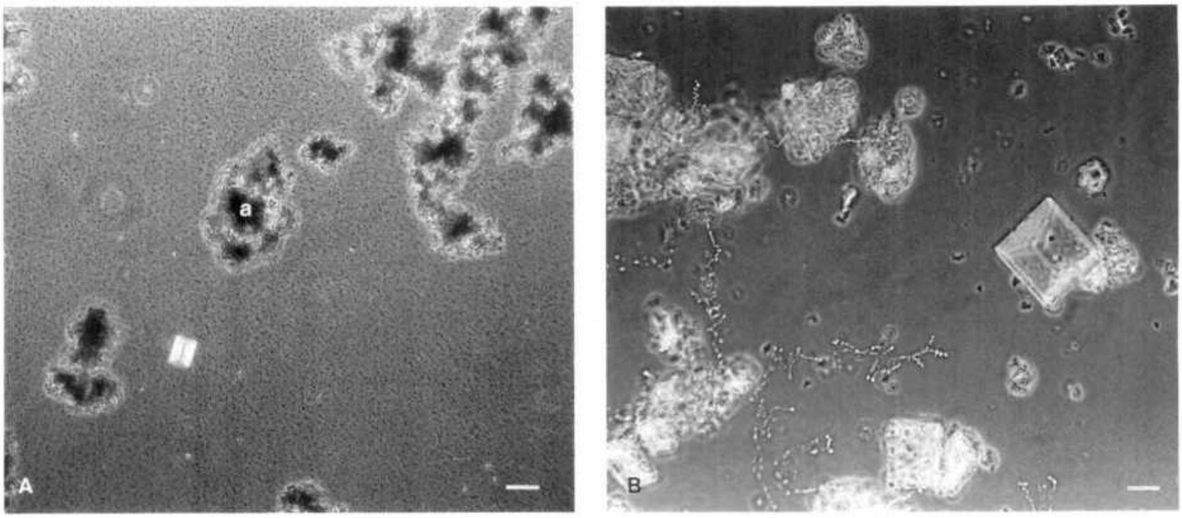

Fig. 3 Crystal habits of struvite formed in the presence of AHA through growth and urease activity of *P. mirabilis* (A) or NH_4OH titration (B). Note the quantity of amorphous material (a) present. Bar represents 40 μm.

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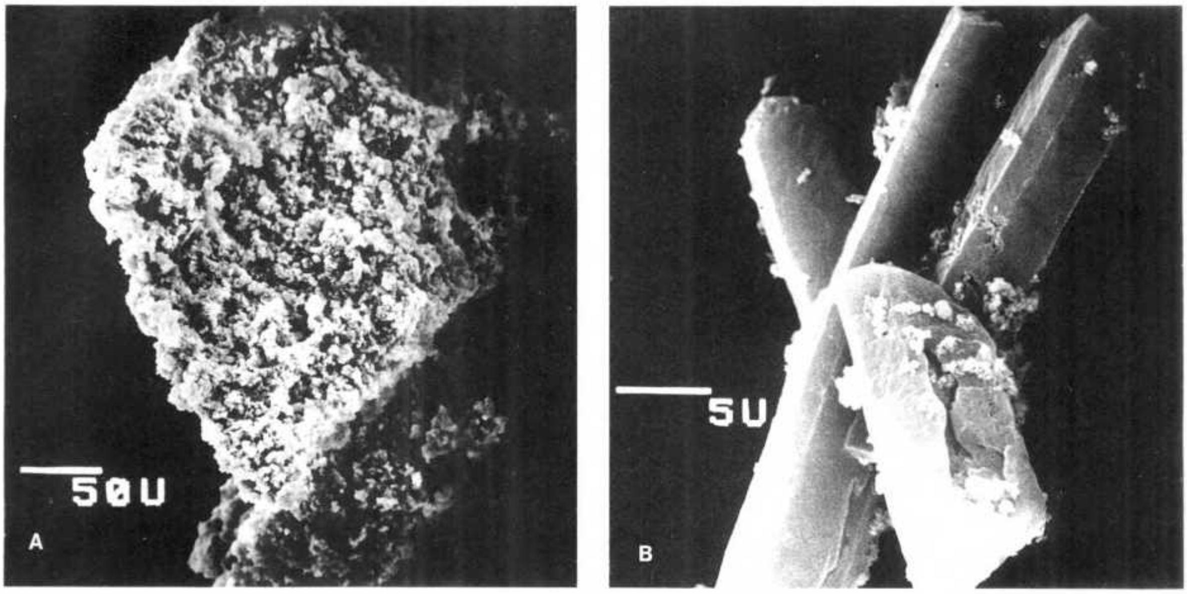

Fig. 4 Struvite formed in the presence of AHA exhibited pronounced pitting of its surface (A). This was not observed in crystals formed in the absence of AHA (B).

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Pyonephrosis: Diagnosis and Treatment

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Summary—A series of 23 confirmed cases of pyonephrosis initially treated by percutaneous nephrostomy drainage were reviewed. Presentation was extremely variable, ranging from sepsis to asymptomatic bacteriuria. Fever, flank pain and leukocytosis were often absent. Ultrasonography was diagnostic in only 3 of 12 patients. In all, 17 patients had associated nephrolithiasis, and 5 patients ultimately required nephrectomy. Renal urine cultures were positive in 16 of 21 instances, with multiple organisms found in 8 of 21, and added bacteriological data not provided by bladder urine cultures in 11 cases. A pre-existing history of urinary tract infection, hypertension and malignancy was common. Percutaneous drainage was a safe, quick and effective diagnostic and therapeutic method.

Pyonephrosis is a serious complication of ureteric obstruction. Unlike pyelonephritis or infected hydronephrosis, pyonephrosis is defined pathologically by gross pus in an obstructed collecting system (Robbins *et al.*, 1984). It is often associated with renal parenchymal destruction and deteriorating function and septic complications, and occasionally requires nephrectomy. Innovations in antibiotics and endourological treatments in the management of urinary infection and stone disease prompted a review of 23 patients with recent episodes of pyonephrosis initially treated with percutaneous drainage. We evaluated their clinical, laboratory and radiological presentation in addition to their management.

Patients and Methods

We studied 23 consecutive patients from May 1986 to October 1990, including 10 males and 13 females, aged 21 to 84 years (median 51 years). Of these, 13 patients presented with sepsis and hydronephrosis with or without an obstructive stone. A further 9 patients had hydronephrosis from an obstructive stone without overt sepsis. In 7 patients an attempted retrograde ureteric stent placement failed. The clinical diagnosis of pyonephrosis was made when pus was aspirated percutaneously from the renal collecting system. Percutaneous drainage was performed with 6F to 14F nephrostomy tubes (median 8F) under ultrasound guidance. All patients received intravenous antibiotics before surgery. Bladder urine cultures were obtained from either voided or straight catheter specimens from 19 patients. Renal urine cultures were collected under sterile conditions from the initial aspirate at percutaneous nephrostomy from 21 patients. Blood cultures were obtained during febrile episodes ($\geqslant$38.5°C) from 12 patients.

All available medical records were reviewed for aetiology and clinical presentation, including symptoms, laboratory and microbiological data, history of endourological manipulation of the involved kidney, complications and follow-up therapy. Culture results were obtained from final microbiology reports. Original radiographic reports from preoperative intravenous urograms, sonograms and/or computed tomograms (CT) were reviewed. Sites of renal obstruction were determined from radiographic data. We define the segments of the ureter as follows: the proximal ureter is between the pelviureteric junction (PUJ) and the upper edge of the sacroiliac (SI) joint; between the upper and lower edge of the SI joint is the mid-ureter; below the lower SI joint to the vesicoureteric junction (VUJ) is the distal ureter.

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Table 1 Aetiology of Ureteric Obstruction Associated with Pyonephrosis

Type of obstruction	*No of patients*
Virgin stones	15
Steinstrasse	2
Ureteric stricture	2
PUJ obstruction	1
Malignancy	3

Table 2 Symptoms and Laboratory Values of Patients with Pyonephrosis

Fever >38°C	15/23
Flank or abdominal pain	13/23
Leukocytosis (WBC $\geqslant 10 \times 10^3/\mu l$)	13/22
Elevated creatinine (Cr >1.3 mg/dl)	12/23
Pyuria (WBC >5/hpf)	18/19
Microhaematuria (RBC >5/hpf)	14/19

Table 3 Microbiology of Pyonephrosis: Culture Results

Organism	*Bladder urine*	*Renal urine*	*Blood*
Enterococcus	4/19	7/21	1/12
E. coli	4/19	5/21	1/12
Candida	2/19	4/21	...
Enterobacter	4/19	2/21	1/12
Klebsiella	3/19	2/21	...
Proteus	1/19	2/21	...
Pseudomonas	3/19	1/21	...
Bacteroides		3/21	
Miscellaneous			
Gram-negative organisms	3/19	4/21	...
Gram-positive organisms	2/19	4/21	...

Table 4 Pyonephrosis: Pre-existing Medical Conditions

Condition	*No. of patients*
Urinary tract infection	9
Hypertension	8
Malignancy	4
Supravesical urinary diversion	3
Nephrolithiasis	3
Neurogenic bladder	3
Diabetes mellitus	2
Vesicovaginal fistula	1
Steroid therapy	1

Results

The causes of ureteric obstruction were identified (Table 1). Staghorn calculi were found in 7 of 23 cases. Calculi including steinstrasse were responsible for 17 of 23 cases. The sites of obstruction were calices (2 of 23), renal pelvis (11 of 23), proximal ureter (2 of 23), mid-ureter (2 of 23) and distal ureter (6 of 23).

The most common symptoms were fever and flank pain. Table 2 shows the laboratory presentation, including leukocytosis, elevated serum creatinine, microhaematuria and pyuria.

Pre-operative radiographic evidence for pyonephrosis was found in 1 of 6 CT scans, and 3 of 12 sonograms of patients with documented pyonephrosis. Delayed excretion and hydronephrosis were noted in 4 of 4 intravenous urograms performed.

Microbiological cultures obtained from blood, bladder, and renal urine are shown in Table 3. Organisms were cultured in 13 of 19 bladder cultures, 16 of 21 renal cultures, and 3 of 21 blood cultures obtained. Multiple organisms were obtained in 4 of 19 bladder and 8 of 21 of renal urine specimens. All multiple organism infections occurred in patients with calculi. In 20 of 23 patients either the bladder or the renal urine samples showed infection. Renal urine cultures showed additional or different organisms from bladder urine in 9 of 19 patients when both were obtained. Organisms were identical for 6 of 19 urine and renal cultures.

Pre-existing medical conditions are listed in Table 4. A history of urinary tract infection and hypertension was most common. A total of 11 of 23 patients were treated previously by extracorporeal shock wave lithotripsy (ESWL) or endourological procedures such as placement of ureteric stents, or percutaneous nephrostolithotomy. Follow-up and definitive therapies were required in 19 of 23 patients. Table 5 shows these procedures.

Table 5 Follow-up and Definitive Treatment after Percutaneous Drainage of Pyonephrosis

Treatment	*No of patients*
ESWL	9
PNL	9
Nephrectomy	5
Ureteroscopic manipulation	3
Ureteric stent	2
Endopyelotomy	1

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Complications occurred in 5 patients as a result of urosepsis, including hypotension and pulmonary oedema in 2 patients and perinephric abscess in 3 patients. Complications secondary to percutaneous nephrostomy tube placement included a perinephric haematoma which required 3 units of blood. Also, 2 patients required nephrostomy tube revision shortly after surgery due to poor drainage. In 1 patient, death resulted from overwhelming rectal haemorrhage caused by radiation proctitis and terminal cervical carcinoma. Hospitalisation ranged from 1 to 34 days (median 7 days).

Discussion

The definition of pyonephrosis is subjective because there is a continuum from infected hydronephrosis to pyonephrosis. Recent definitions of pyonephrosis have been based on the presence of pus in the renal collecting system (Jimenez *et al.*, 1978; Coleman *et al.*, 1981; Subramanyam *et al.*, 1983; Jeffrey *et al.*, 1985). Using this criterion, pyonephrosis was found to be a highly variable syndrome which was difficult to diagnose in the limited number of patients studied. Clinically, patients presented with a variety of complaints ranging from asymptomatic bacteriuria to urosepsis complicated by hypotension and/or perinephric abscess. Pain, fever and leukocytosis were absent in 4 patients. Bladder urine cultures were negative in a third of patients. Hydronephrosis and pyuria were universal, however. Radiographic investigations were most often non-diagnostic. Although reports of sonographic sensitivity for the correct diagnosis of pyonephrosis have ranged from 62% to 90% (Jeffrey *et al.*, 1985; Subramanyam *et al.*, 1983), ultrasonography correctly diagnosed only 3 of 12 cases of pyonephrosis in this series. Previous reports of pyonephrosis have lacked confirmation by pathological or urine aspiration in all cases (Jeffrey *et al.*, 1985). CT scans and urograms were less helpful. We agree with Jeffrey *et al.* (1985), who recommended a "cautious approach" to sonographic diagnosis because of the non-specific and variable appearance of pyonephrosis (Coleman *et al.*, 1981; Subramanyam *et al.*, 1983). In summary, there were no clinical, laboratory or radiographic indicators which distinguished pyonephrosis from hydronephrosis. Renal urine aspiration was the only diagnostic method.

Patients potentially at risk of infected hydronephrosis were those with histories of calculi, recurrent urinary infections, ESWL, endourological procedures, and ileal loop urinary diversion. Risk factors must be included in the diagnostic equation since symptoms, laboratory and radiographic information are often non-diagnostic.

Renal and bladder urine cultures were remarkable for a vareity of organisms, without the predominance of *Proteus* and *Escherichia coli* noted by others (Silverman and Stamey, 1983; Jeffrey *et al.*, 1985). Multiple and unusual organisms, including anaerobes and *Candida* may reflect the changing flora facing urologists. These infections may be chronic and associated with calculi. Poor function of the involved kidney may prevent the achievement of adequate antibiotic levels in the infected urine. Along with repetitive use of antibiotics, poor renal function may contribute to the development of resistant strains and the presence of unusual organisms. Pre-operative antibiotics given just before percutaneous drainage may have inhibited culture growth of the more common pathogens in this study.

Renal cultures provided microbiological information not found in bladder cultures in 11 cases. Bladder urine specimens from urinary diversions and reservoirs, indwelling bladder catheters, or urinary fistula are often contaminated, making renal cultures indispensable. Antibiotics may inhibit bladder urine culture growth despite significant infection in an obstructed kidney, causing 6 of 19 bladder cultures in our series to be negative. Complete ureteric obstruction may also prevent upper tract micro-organisms from infecting the bladder.

Percutaneous nephrostomy drainage was a successful and safe procedure with only a single significant operative complication, a perinephric haematoma. Neither large calibre nephrostomy tubes nor irrigation were necessary to achieve adequate drainage.

Percutaneous access and drainage offers many advantages over retrograde techniques. It is quick and requires only ultrasound guidance and local anaesthesia. Retrograde techniques are often difficult. For example, percutaneous nephrostomies avoid retrograde difficulties from enlarged obstructive prostates, a pregnant uterus, urinary diversions, impassable ureteric obstructions, unidentifiable ureteric orifices and lithotomy positioning. In this series, 7 patients failed a retrograde attempt prior to percutaneous drainage. Percutaneous drainage can be followed easily. Nephrostomy catheters offer long-term drainage for unstable or terminal patients and provide upper tract access for others undergoing definitive therapy with percutaneous nephrostolithotomy (PNL) or ESWL. Antegrade nephrostography offers excellent visualisation of the collecting system and ureter. Finally antegrade internalisation of nephrostomy tubes can often be accomplished later.

Previous reports emphasise the role of nephrectomy as definitive therapy for patients with pyonephrosis (Blandy and Singh, 1976; Jimenez *et al.*, 1978; Penter and Arkell, 1989). In this series, nephrectomy was needed in only 5 patients. This may reflect improvement in antibiotics, percutaneous drainage and definitive endourological therapies including PNL, ESWL and ureteroscopic techniques. Once free of obstruction, infection and stones, kidney function may improve. However, preservation of renal function may be particularly important in patients with hypertension, diabetes, recurrent calculi, and those requiring chemotherapy for malignancy who may expect future deterioration of the uninvolved kidney. It is not known whether, after definitive treatment, the affected kidney contributes significantly to overall renal function or is a source of morbidity later.

Pyonephrosis is a variable syndrome associated with both acute and chronic illness. The clinical presentation is often indistinguishable from hydronephrosis. Some patients may be virtually asymptomatic. High suspicion is most important for successful diagnosis. Ultrasonographic evaluation is suggestive, but often fails to detect signs of pyonephrosis. Percutaneous nephrostomy drainage is a safe and rapid method that is diagnostic and therapeutic. It offers unique bacteriological information and management advantages over retrograde ureteric stents.

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Does DNA Flow Cytometry Give Useful Prognostic Information in Renal Parenchymal Adenocarcinoma?

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Summary—DNA ploidy and S-phase fraction (SPF) were measured by flow cytometry on 381 paraffin blocks from 93 unselected primary renal parenchymal adenocarcinomas (RPA). The results were compared with tumour grade and T category and patient survival, with a mean follow-up of 87 months. Only 21% of the tumours were uniformly diploid and ploidy was heterogeneous in 49% of cases. DNA ploidy and SPF were significantly associated with grade, but not T category of disease. Both flow cytometric parameters were significantly related to survival in a univariate analysis. However, when tumour grade was taken into account, both DNA ploidy and SPF lost their prognostic significance. Thus, neither of these parameters gave prognostic information additional to that provided by tumour grade in unselected cases of primary RPA.

The prognosis of renal parenchymal adenocarcinoma is associated with the stage and grade of the primary tumour (Robson *et al.*, 1969; Medeiros *et al.*, 1988). DNA ploidy provides another prognostic indicator in many types of cancer, but its significance in RPA is unclear.

Despite many studies of DNA ploidy in RPA (Bennington and Mayall, 1983; Chin *et al.*, 1985; Baisch *et al.*, 1986; Ljungberg *et al.*, 1986a, b, c, 1987, 1988; Ekfors *et al.*, 1987; Rainwater *et al.*, 1987; DeKernion *et al.*, 1989; Grignon *et al.*, 1989a, b) it is debatable whether DNA ploidy provides useful clinical information. Comparison of the data is difficult for 3 main reasons. Firstly, many studies use selected groups of patients, chosen either by stage, grade or treatment, often with short follow-up periods. Secondly, 2 methods have been used to measure DNA content, flow cytometry and single cell cytophotometry and results from these are not directly comparable. Thirdly, DNA content is exceptionally heterogeneous in RPA, yet many studies rely on either a single sample or bulked material. The aim of this study was to investigate the prognostic significance of DNA ploidy and S-phase fraction measured by flow cytometry in a large series of primary RPA treated by nephrectomy and with a long mean follow-up period, analysing all available samples from each tumour separately.

Patients and Methods

All patients presenting with RPA and treated by nephrectomy in the St Peter's group of hospitals during the period 1955–1979 were included in the study. Paraffin-embedded material was available for 93 patients, of whom 69 were male. The age range was 33–85 years (mean 60). In all, 35 patients remained disease-free for periods of up to 20 years, of whom 22 were followed for a minimum of 5 years. The mean period of follow-up was 87 months. All of the tumours were graded by 1 experienced histopathologist using a system which included assessment of the degree of acinar or papillary formation, cytological pleomorphism and frequency of mitoses (Griffiths and Thackray, 1949). Where these findings varied in different areas of a neoplasm, the highest grade seen was allocated.

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Each tumour-containing paraffin-wax block from every case was analysed separately. Sections 40 μm thick were cut and the nuclei extracted using a modification (Camplejohn *et al.*, 1989) of the method described by Hedley *et al.* (1983). The nuclei were stained with 1 μg/ml DAPI (4′6-diamino-2 phenylindol-hydrochloride; Boehringer Mannheim, Germany). A minimum of 10,000 nuclei from each sample were analysed on a Becton Dickinson FACS Analyzer. The DNA index was calculated relative to the normal G0/G1 peak, an index of 1.0 indicating that only diploid nuclei were present. An index >1.0 indicated the presence of an aneuploid peak in addition to the diploid peak. Samples with an index of 1.9 or 2.0 were categorised separately as tetraploid. The fraction of cells in the S-phase of the cell cycle was calculated as described by Camplejohn *et al.* (1989). DNA ploidy was measurable in 88 of 93 (95%) cases in at least 1 block, using the criterion of a coefficient of variation (CV) <11.0%. The number of blocks available ranged from 1–10, totalling 381, with an average of 4.1 blocks per patient. DNA ploidy was measurable in 305 of 381 (80%) blocks.

Chi-squared analysis was used to assess differences between sub-groups of patients. Survival curves were plotted using the Kaplan-Meier method and the logrank test was used to compare the survival of different groups of patients. Survival curves adjusted for imbalances in prognostic factors were drawn using the method described by Gregory (1988).

Results

DNA ploidy was measured in 88 primary RPA, of which 21 (24%) were diploid, 12 (14%) tetraploid and 55 (62%) aneuploid. DNA ploidy was heterogeneous in 43 (49%) of the tumours: 6 had diploid and tetraploid blocks, 12 diploid/aneuploid, 14 tetraploid/aneuploid and 11 had blocks which yielded examples of all 3 types of DNA histogram. DNA ploidy was homogeneous in the remaining 45 cases, of which 21 were diploid, 6 tetraploid and 18 aneuploid. However, the results may underestimate the degree of heterogeneity, as only 1 block was assessable from 11 of 45 of these tumours. SPF could be calculated for 83 tumours. The median SPF was 7.9% (range 1.6–32.7).

Using the UICC (1978) staging system, 9 (10%) of the tumours were T1, 24 (27%) T2 and 55 (63%) T3. As shown in Table 1, there was no statistically significant relationship between category and either DNA ploidy ($P=0.44$) or SPF ($P=0.22$). The tumours were classified by 1 histopathologist into 4 (5%) grade 1, 66 (75%) grade 2 and 18 (20%) grade 3 (Table 2). An increased incidence of DNA aneuploidy was seen in high grade tumours but the association between grade and DNA ploidy did not reach statistical significance ($P=0.08$). Tumour grade, however, correlated strongly with SPF ($P=0.007$), with 14 of 17 grade 3 tumours having an SPF above the median while all grade 1 tumours had an SPF below the median. DNA ploidy was also significantly related to SPF, with 38 of 42 aneuploid tumours having an SPF above the median (Table 3).

Table 1 DNA Ploidy and SPF versus T Category

	T1	*T2*	*T3*	
Diploid	2	8	11	
Aneuploid	7	16	44	$P=0.44$
SPF≤7.9	5	14	22	T1+T2 versus T3
SPF>7.9	4	9	29	$P=0.22$

Table 2 DNA Ploidy and SPF versus Tumour Grade

	Grade 1	*Grade 2*	*Grade 3*	
Diploid	3	17	1	Grade 1+2 versus 3
Aneuploid	1	49	17	$P=0.08$
SPF≤7.9	4	34	3	
SPF>7.9	0	28	14	$P=0.007$

Table 3 DNA Ploidy versus SPF

	Diploid	*Aneuploid*	
SPF≤7.9	17	24	
SPF>7.9	4	38	$P=0.002$

There was no significant difference in survival between patients with T1 and T2 disease ($P=0.9$), but patients with T3 tumours had a significantly poorer prognosis (T1 and T2 versus T3, $P=0.003$) (Fig. 1). Survival was strongly influenced by tumour grade (grade 1 versus grade 2, $P=0.025$; grade 2 versus grade 3, $P<0.001$) (Fig. 2). None of the 4 patients with grade 1 tumours died, whereas 15 of 18 of those with grade 3 tumours were dead within 2 years.

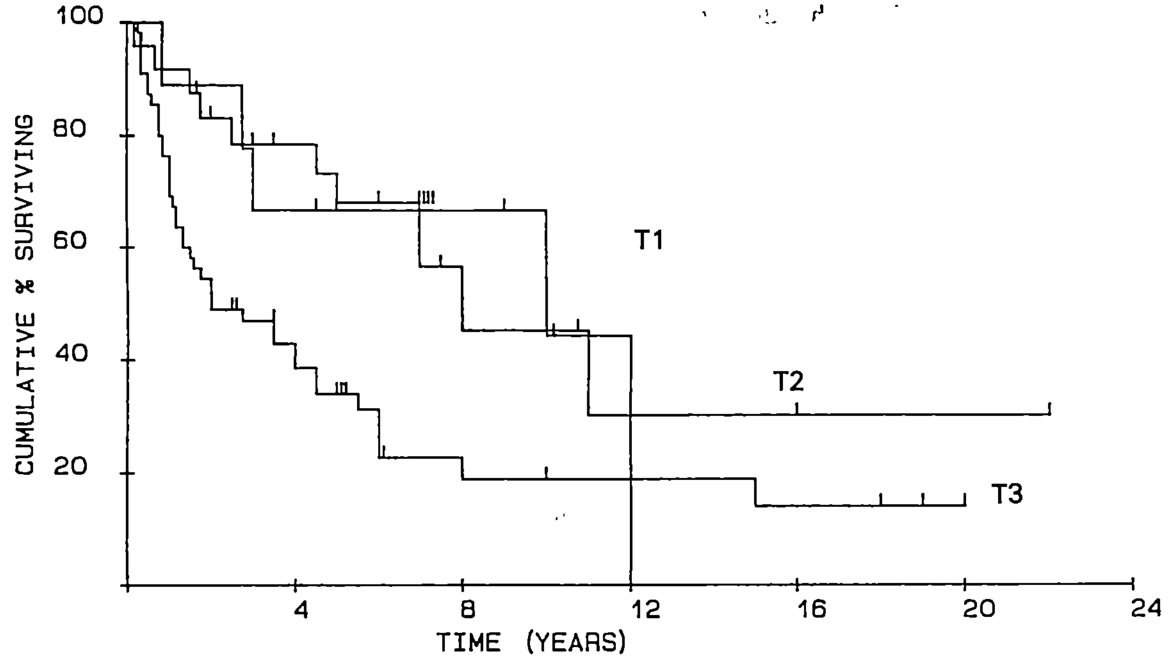

Fig. 1 Cumulative survival versus T category.

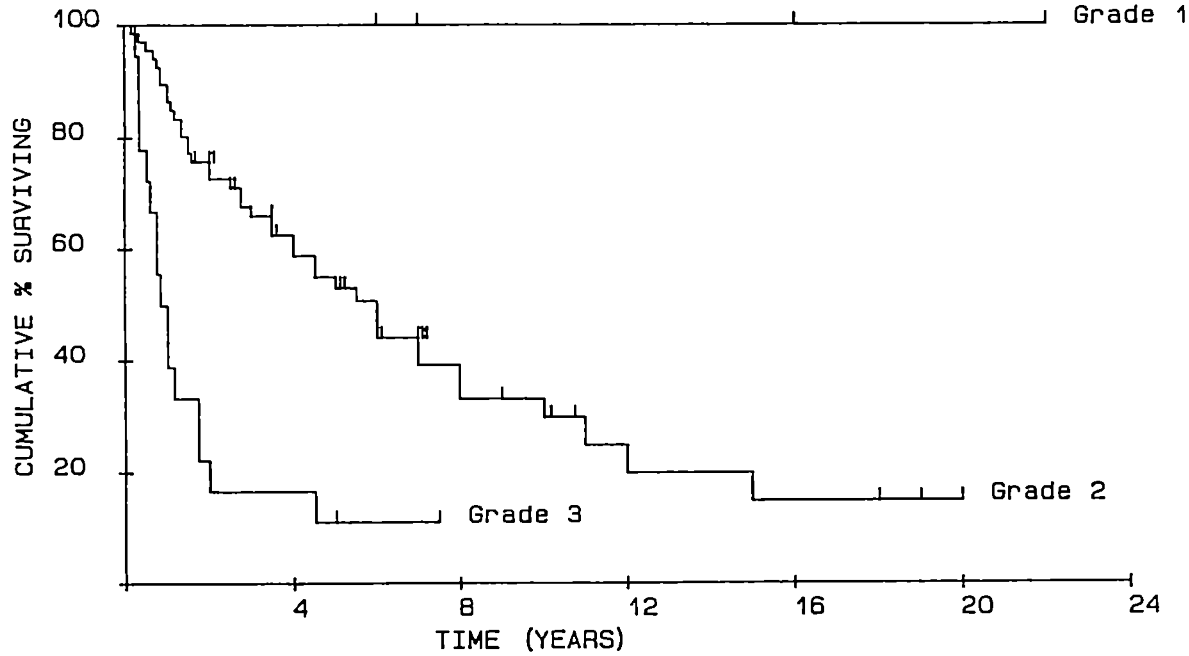

Fig. 2 Cumulative survival versus tumour grade

Diploid tumours were associated with a slightly better prognosis than aneuploid tumours ($P=0.03$) (Fig. 3). There was no difference in survival between patients whose tumours were tetraploid and those with other aneuploid tumours. DNA ploidy levels were heterogeneous in 49% of the tumours. The presence of diploid or tetraploid elements in an aneuploid tumour did not influence prognosis.

When comparing ploidy with other variables, tumours heterogeneous for ploidy were assigned to the most abnormal pattern.

When patients were divided into sub-groups using the median value of SPF 7.9% as a cut-off, those in the high SPF group had a shorter survival ($P=0.02$) (Fig. 4). As SPF was strongly correlated with tumour grade, the survival curves were adjusted for this relationship using the method described by Gregory (1988). This method provides a graphical counterpart to Mantel's adjusted chi-square statistic and allows curves to be drawn as they would have been expected to look, had other prognostic factors been distributed evenly between the groups. When survival curves for patients whose tumours had high or low SPF were compared using this method, and adjusted for the uneven distribution of tumour grade between the 2 groups, SPF no longer significantly influenced survival (Fig. 5). Similarly, DNA ploidy lost its significance as a prognostic factor when the survival curves were adjusted for imbalance in the distribution of T category (adjusted $P=0.47$). Thus, this form of multivariate analysis suggests that the poor prognosis noted for patients whose tumours have a high SPF or are aneuploid is largely attributable to the strong association between both SPF and DNA ploidy and tumour grade.

Discussion

In this study both DNA ploidy and SPF were significantly associated with each other and with prognosis in univariate analyses. However, when allowance was made for tumour grade, neither flow cytometrically determined parameter retained its prognostic significance. Thus, it would seem that DNA flow cytometry has little to offer, in addition to tumour grade, in predicting the clinical outcome for individual patients.

In line with the findings in this work, the majority of published studies have found an association between DNA ploidy and survival (Baisch *et al.*, 1986; Ljungberg *et al.*, 1986c; DeKernion *et al.*, 1989; Grignon *et al.*, 1989a, b). However, some authors failed to demonstrate such an association (Chin *et al.*, 1985; Ljungberg *et al.*, 1986a; Ekfors *et al.*, 1987). These discrepancies probably result from a variety of technical and statistical differences between the various studies. For example, many studies used selected patients, chosen according to stage, grade or treatment, had follow-up periods of less than 5 years and used different methods for measuring DNA ploidy. Also, most studies either rely on a single representative sample or bulk material and make 1 measurement of DNA ploidy. It is clear from this and previous studies (Ljungberg

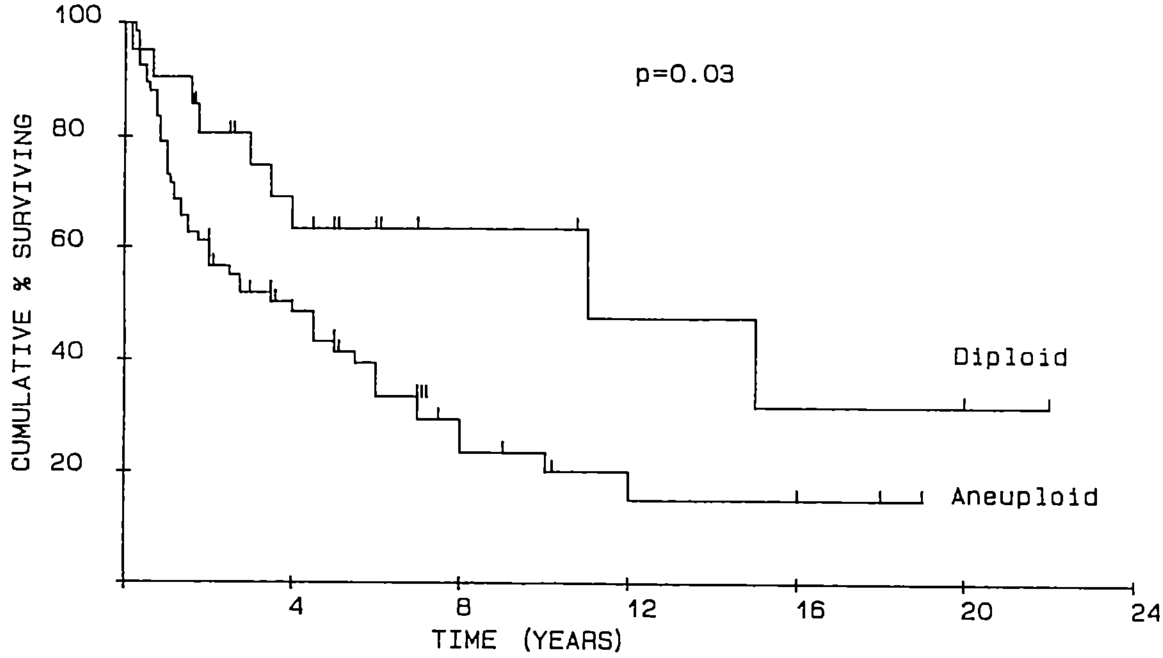

Fig. 3 Cumulative survival versus DNA ploidy.

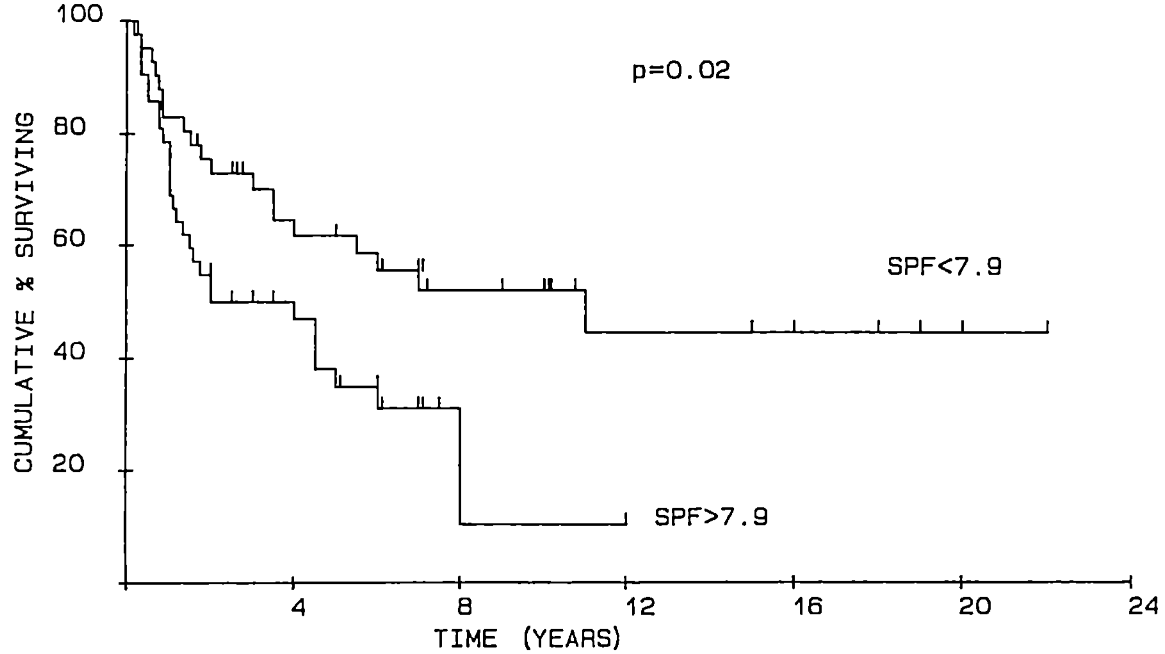

Fig. 4 Cumulative survival versus S-phase fraction (SPF). Tumours were divided into 2 groups using the median value of SPF (7 9%)

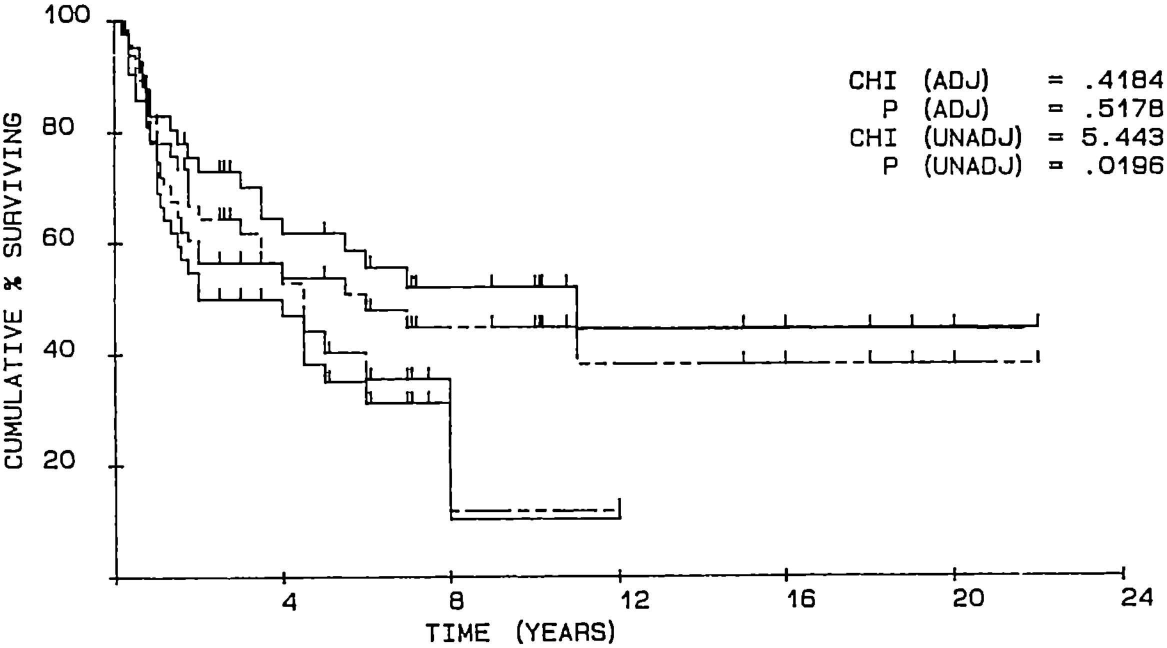

Fig. 5 Cumulative survival versus SPF adjusted for the uneven distribution of tumour grade between the low and high SPF subgroups. The upper pair of lines represent data for the low SPF sub-group and the lower pair of lines the data for the high SPF subgroup In each case the solid line refers to the unadjusted data as shown in Fig. 4 and the dashed line represents the adjusted SPF data

et al., 1986c, 1988) that RPA is exceptionally heterogeneous with respect to DNA ploidy, and that a single sample would not be representative in ≥50% patients.

DNA ploidy was not associated with T category, in agreement with some authors (Frankfurt *et al.*, 1984; Ljungberg *et al.*, 1986a, 1988; Ekfors *et al.*, 1987) but not others (Ljungberg *et al.*, 1986b; Rainwater *et al.*, 1987; Grignon *et al.*, 1989b). The lack of agreement is probably due again to patient selection, short follow-up, inadequate sampling and differences in technology.

Various methods are used to grade RPA, some histological and others based on nuclear appearance alone. All methods correlate with prognosis. In the present investigation, in which the highest grade was compared with the most abnormal ploidy pattern, we found an association between DNA ploidy and grade, as have most other authors, although there are some exceptions (Frankfurt *et al.*, 1984; Chin *et al.*, 1985; Ekfors *et al.*, 1987). The majority of tumours in this study were moderately well differentiated, a classification of little help in clinical management, but subdividing the grade 2 tumours according to DNA ploidy did not improve the prognostic discrimination.

An estimate of the proportion of nuclei synthesising DNA, the S-phase fraction, can be obtained from the DNA histogram. Such calculations rely on many assumptions, so that little reliance can be placed on the absolute values, although it is probably valid to classify the tumours into those with low or high proliferative activity. SPF was, as described previously, prognostic in a univariate analysis but this discrimination was lost when tumour grade was taken into account.

It would seem that both DNA ploidy and SPF have prognostic significance but that this is due to their strong association with tumour grade, to which they have little to add.

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Increase in Presumptive Sensory Nerves of the Urinary Bladder in Idiopathic Detrusor Instability

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Summary—The density of subepithelial, presumptive sensory nerves in the bladder wall was assessed in 21 women with idiopathic detrusor instability and compared with the density of these nerves in 21 asymptomatic women, using a point-counting technique on sections of bladder biopsies stained for acetylcholinesterase activity. The mean value (±S.E.) for the amount of such nerves in patients with detrusor instability ($91 \pm 13/\text{mm}^2$) was significantly greater than that from the control group ($61 \pm 7/\text{mm}^2$). This suggests that a relative abundance of subepithelial sensory nerves may serve to increase the appreciation of bladder filling, giving rise to the frequency and urgency of micturition which are characteristic of patients with detrusor instability.

Despite the fact that idiopathic detrusor instability affects up to one-third of all women with urinary incontinence (Abrams *et al.*, 1983), the aetiology of this condition remains unknown. Such patients typically present with urgency and frequency of micturition. However, the possibility that these symptoms may be associated with an enhanced sensory input from the bladder wall has not been investigated morphologically.

A plexus of presumptive sensory nerves has been described beneath the epithelium of the human urinary bladder which may be demonstrated using a staining technique for acetylcholinesterase (Gosling *et al.*, 1983; Dixon and Gilpin, 1987). The purpose of the present study was to assess the density of this acetylcholinesterase-positive subepithelial nerve plexus in a group of women with urodynamically proven idiopathic detrusor instability compared with a group of asymptomatic age-matched controls. In this way it was hoped to determine whether there is any morphological evidence to support the possibility that an increased sensory innervation is associated with idiopathic detrusor instability.

Patients and Methods

A series of 21 females (mean age 56 years, range 43–77) with long-standing urodynamically proven idiopathic detrusor instability underwent endoscopic cold cup bladder biopsy. Control females with haematuria, but no urgency or frequency of micturition (mean age 56 years, range 29–81), were biopsied in the same way. In view of the known regional variation in subepithelial nerve distribution (Gosling *et al.*, 1983), all specimens were taken approximately 2 cm lateral and 2 cm cephalad to the ureteric orifice.

Biopsies were rapidly frozen in isopentane cooled in liquid nitrogen and stored at −80°C. Cryostat sections of 10 fm thickness were stained for acetylcholinesterase using a modification of Gomori's method (1952). For each patient at least 10 non-overlapping fields immediately below the intact epithelium were studied using a final magnification of ×400. Sections were examined using a calibrated eyepiece graticule aligned parallel to the base of the epithelium. Both the total number of nerve fibres within the grid and the number of nerve fibres which crossed the intersecting grid lines (a technique known as "point counting") were assessed blindly by the first 2 authors. An inter-observer mean of the total and "point" counts for

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the 10 fields from each patient was then calculated. After assessing the normality of distribution of these data using Filliben's method (Wainwright and Gilbert, 1981), the means for patients and controls were compared using Students's *t* test.

Results

The region examined for subepithelial nerves extended from the base of the epithelium to a depth of 0.15 mm (Fig.), thus excluding the perivascular nerve plexuses that are frequently associated with the larger submucosal blood vessels which lie at deeper levels in the submucosa. The mean point count (±S.E.) of enzyme-positive subepithelial nerves for unstable patients was $91 \pm 13/\text{mm}^2$, a value significantly greater at the 5% level than that obtained for control subjects ($61 \pm 7/\text{mm}^2$; $P = 0.025$) (Table). The values for the total nerve counts, while not statistically significantly different, showed the same trend, a higher value (295 ± 34) being obtained for the unstable patients compared with 254 ± 26 for the controls.

However, whereas the total nerve counts varied considerably from region to region within the 10 fields counted in each specimen, the point counts, which give an expression of the amount of nerve per unit area, were generally more consistent within the 10 fields examined for each patient.

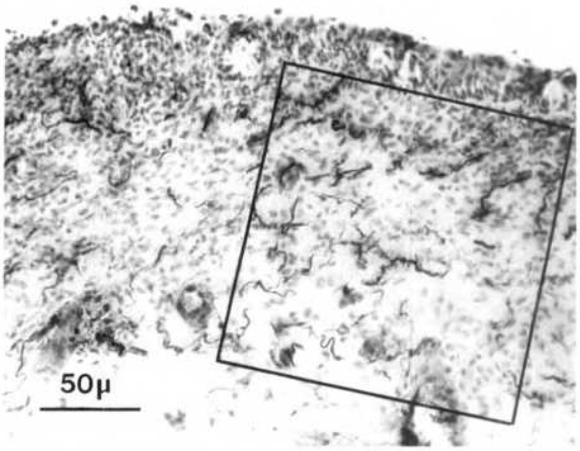

Fig. Biopsy from a patient with detrusor instability showing the subepithelial plexus of acetylcholinesterase-positive nerve fibres. The square indicates a typical area of the subepithelial connective tissue that was assessed by point counting (× 256).

There was no correlation between the age of the patient and either the total nerve count or the point count for either controls or unstable patients.

Table Point-counting Studies of Patients and Controls

	Patients with idiopathic instability			*Controls*		
Patient no.	*Age (years)*	*Point count (per mm²)*	*Total number of nerve profiles (per mm²)*	*Age (years)*	*Point count (per mm²)*	*Total number of nerve profiles (per mm²)*
1	49	195	540	69	119	502
2	48	124	297	29	44	200
3	61	222	437	59	51	232
4	70	101	335	39	53	274
5	43	34	206	61	47	205
6	50	15	64	69	72	363
7	44	61	288	60	84	335
8	55	177	530	74	85	212
9	50	107	253	68	136	466
10	63	123	354	39	52	261
11	47	40	70	30	84	350
12	48	109	245	73	64	372
13	62	72	244	47	35	241
14	52	87	360	65	112	292
15	54	88	472	60	53	181
16	77	12	139	32	45	101
17	69	15	80	81	14	30
18	57	63	220	52	35	181
19	56	34	141	63	8	65
20	63	170	582	80	42	217
21	60	68	330	29	52	265
mean	56	91	295	56	61	254
S.E.		±13	±34		±7	±26

Discussion

The results of the present study have shown that the amount of acetylcholinesterase-positive subepithelial nerves in the urinary bladder is increased in patients with idiopathic detrusor instability compared with controls. This difference was statistically significant when using the values obtained by point counting. The same trend was seen when the results of total nerve counts were compared, although the difference did not reach significance since values for total counts fluctuated widely among the 10 fields examined for each patient.

Nerves forming the subepithelial plexus of the human urinary bladder are unrelated to recognised neuro-effector target sites and are therefore considered to represent the terminations of afferent sensory neurons (Gosling *et al.*, 1983). Furthermore, subepithelial nerves of the human urinary bladder have been shown to contain substance P (Islam *et al.*, 1983), a well recognised constituent of primary afferent sensory fibres (Burnstock, 1986). In addition, the fine structure of the subepithelial axonal varicosities has been shown to differ in several respects from typical cholinergic effector terminals, such as occur in profusion among the detrusor smooth-muscle cells (Dixon and Gilpin, 1987). The fact that the subepithelial nerves run close to the base of the urothelium, and in some instances actually penetrate between the epithelial cells, suggests that they function to convey sensory information from the bladder mucosa. As yet the precise nature of this sensory information remains unknown. The subepithelial nerve terminals may register touch, pain or temperature, or possibly act as stretch receptors which are stimulated as the bladder fills. Thus the finding that such nerves are relatively abundant in patients with detrusor instability may explain, in part, the increased appreciation of bladder filling giving rise to the urgency and frequency of micturition which are so characteristic of such patients.

A previous study of female patients with idiopathic detrusor instability (Gu *et al.*, 1983) focused on the detrusor muscle and demonstrated a relative paucity of vasoactive intestinal polypeptide (VIP) as measured by radioimmunoassay. VIP is believed to act as a neuromodulator with an inhibitory role in the control of detrusor contractile activity (Kinder and Mundy, 1985). More recently a significant decrease in the density of muscarinic receptors, together with an increase in the density of alpha-adrenergic receptors, has been reported in cases of detrusor hyper-reflexia (Restorick and Mundy, 1989). While such studies provide insight into the altered excitatory control of the unstable detrusor muscle, the present study has shown that an increased afferent innervation of the bladder mucosa may also be a significant factor in the aetiology of detrusor instability.

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Loss of Sensory Neuropeptides in the Obstructed Human Bladder

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Summary—This is the first investigation of alterations in the innervation of the obstructed human bladder by nerves containing neuropeptides. The patient groups studied were those with stable detrusor function, those with unstable detrusor function, and those presenting with acute retention of urine. Specimens of bladder tissue were taken from the lateral wall of the bladder below the peritoneal reflection. A total of 23 patients was studied (control, n = 4; acute retention, n = 5; stable obstruction, n = 5; unstable obstruction, n = 9). Substance P, calcitonin gene-related peptide and vasoactive intestinal polypeptide levels in the bladder were quantified by immunoassay. The density of innervation of the bladder detrusor by nerves containing these neurotransmitters and by those containing neuropeptide Y and somatostatin was assessed using both semiquantitative and quantitative immunohistochemical techniques.

A reduction in the density of innervation by vasoactive intestinal polypeptide, calcitonin gene-related peptide, substance P and somatostatin-immunoreactive but not neuropeptide Y-immunoreactive nerve fibres was shown in the obstructed bladder. These findings, combined with the significant reduction in substance P content of the obstructed bladder and in particular of the acute retention bladder, indicate that there may be an afferent nerve dysfunction resulting from prostatic bladder outflow obstruction.

The human bladder body receives a dense parasympathetic innervation comprised predominantly of acetylcholine-containing nerves (Gosling *et al.*, 1983), in contrast to the sympathetic noradrenaline-containing nerves which are sparse and non-uniform (Sundin *et al.*, 1977; Benson *et al.*, 1979). Co-ordinated contraction of the urinary bladder at the time of micturition is initiated and maintained by parasympathetic nervous stimulation via the pelvic nerves in man and all mammalian species studied (Andersson and Sjögren, 1982). Conversely, there is no evidence to support a significant primary role for the sympathetic nervous system in the control of human bladder filling (Awad *et al.*, 1974; Jensen, 1981). Langley and Anderson (1895) first reported partial atropine-resistance during electrical stimulation of the sacral roots to the dog bladder; however it was not until the early 1970s that the concept of non-adrenergic non-cholinergic (NANC) neurotransmission in the bladder was introduced (Ambache and Zar, 1970; Burnstock, 1972; Taira, 1972). Whilst it is widely accepted that adenosine 5′-triphosphate (ATP) is a co-transmitter used by NANC excitatory nerves in the rodent urinary bladder (Burnstock, 1972; Fujii, 1988; Bo and Burnstock, 1990), it is only recently that *in vitro* pharmacological studies have demonstrated a small purinergic component in the human bladder in response to electrical field stimulation (Hoyle *et al.*, 1989). Although it is a matter of debate as to whether the atropine-resistant, tetrodotoxin-sensitive component plays a significant physiological role in normal human detrusor function (Husted *et al.*, 1983; Sibley, 1984), it seems more likely that NANC neurotransmission may be of greater importance in the functionally disturbed bladder (Sjögren *et al.*, 1982).

A number of neuropeptides have been localised

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in the mammalian urinary bladder wall (Larsson *et al.*, 1977; Gu *et al.*, 1984; Crowe and Burnstock, 1989). Neuropeptide Y (NPY) is localised in sympathetic nerves, particularly around blood vessels, whilst non-sympathetic NPY-containing nerves innervate the bladder smooth muscle (Mattiasson *et al.*, 1985) and NPY is often co-localised with somatostatin in intrinsic nerves in the bladder wall (James and Burnstock, 1989). Vasoactive intestinal polypeptide (VIP) is found in parasympathetic nerves and projections from intrinsic ganglia and has also been co-localised with substance P (SP) in sensory afferent nerve fibres (De Groat *et al.*, 1986). Calcitonin gene-related peptide (CGRP) and SP are contained in sensory-motor nerves (Sundler *et al.*, 1985; De Groat *et al.*, 1986; Yokokawa *et al.*, 1986). The human bladder also contains all of these neuropeptides (Larsson *et al.*, 1977; Gu *et al.*, 1983a, 1984; Crowe *et al.*, 1991). This quantitative study was designed to investigate the normal histological distribution of these neuropeptides, which may act as neurotransmitters and/or neuromodulators, and to document the changes that occur in association with bladder outflow obstruction.

Patients and Methods

Bladder tissue was obtained at the time of prostatectomy from the lateral walls of the bladder dome below the peritoneal reflection. In patients undergoing transurethral surgery a partial-thickness cup biopsy was taken and a full-thickness biopsy was taken in those undergoing open surgery. The study population comprised patients undergoing surgery for the relief of benign prostatic outflow obstruction and in whom there was no evidence of renal dysfunction or co-existing prostatic neoplasia. All patients underwent full pre-operative urodynamic assessment using the technique of videocystometry (Bates *et al.*, 1970), thereby allowing pre-operative subdivision of separate groups. This study was carried out with full informed consent, following approval by the local ethical committee.

The groups submitted to histological analysis were as follows: stable obstruction n = 5, mean age 65.80 ± 2.56 years; unstable obstruction n = 9, mean age 67.44 ± 2.69 years; acute retention n = 5, mean age 69.40 ± 3.49 years. In addition, tissue was obtained from the bladders of unobstructed patients undergoing other surgical procedures. These patients had normal flow rates, no residual urine on post-voiding ultrasound and there was no clinical or histological evidence of bladder outflow obstruction (n = 4, mean age 56.00 ± 7.78 years). In the absence of symptoms a more detailed urodynamic assessment was not possible. In order to exclude a histological abnormality such as collagenous infiltration or detrusor muscle hyperplasia or hypertrophy, separate bladder biopsies from these patients were submitted to a full histological and morphometric analysis. Although the mean age of the control population was less than that of the obstructed patients, the difference was not statistically significant at the 5% level.

The groups submitted for biochemical assay included those of the above patients where sufficient tissue was available and were comprised as follows: stable obstruction n = 3, mean age 64.79 ± 2.34 years; unstable obstruction n = 6, mean age 65.32 ± 2.21 years; acute retention n = 6, mean age 68.71 ± 3.58 years; control n = 4, mean age 56.00 ± 7.78 years.

Tissue preparation for histological analyses

Each biopsy specimen was immediately fixed to a small piece of cork with a tissue-mounting solution.

(i) Some of the tissue was then immediately frozen in theatre in isopentane (2-methylbutane), which had been previously cooled in liquid nitrogen to −160°C. The frozen tissue was then stored at −70°C, and transported to laboratories either packed on dry ice or in liquid nitrogen and again stored at −70°C. In the laboratory, the material was removed from the −70°C refrigerator and allowed to equilibrate for 5 min in a −20°C cryostat. Serial sections were cut from each tissue block with a microtome at thicknesses of 10–20 µm. Tissue was sectioned and stained for routine histology using Masson's trichrome technique (Masson, 1929).

(ii) Other tissue collected for specific immunohistochemistry was fixed rapidly in 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS), pH 7.1–7.4 for 1.5 h at room temperature, rinsed in PBS containing 7% sucrose and 0.1% sodium azide, and left overnight at 4°C in the same buffer.

Histological techniques

Routine histology. Masson's trichrome technique (Masson, 1929) was used. Quantitative assessment of the proportion of muscle and connective tissue within 10 representative fields from each section was carried out with a graticule counting technique, with additional assessment of muscle cell size which allowed correction of the results for muscle hypertrophy and hyperplasia (Gosling *et al.*, 1986).

Immunohistochemistry. The tissue sections (10 μm) were cut on a cryostat and immunofluorescence staining was carried out using the indirect method (Coons *et al.*, 1955). The sections were incubated for 18 h at room temperature with antisera raised in rabbits to NPY, VIP, SP, CGRP and somatostatin (all from RIA, UK) at a dilution of 1 in 1000 (VIP) and 1 in 200 for the remaining antisera, then rinsed in PBS and incubated for 1h at room temperature with fluorescein isothiocyanate conjugated sheep anti-rabbit immunoglobulin G (Nordic) at a dilution of 1 in 100. After a further wash in PBS, the sections were mounted in PBS-glycerol (1:1) and examined using a Zeiss fluorescence microscope fitted with epi-illumination. Control sections were incubated with either normal rabbit serum, or the antiserum pre-absorbed with the substance under investigation.

Quantitative methods for light microscopy. All sections were coded prior to processing and staining and were examined by the observer in a blind fashion, the results for each patient being derived from the analysis of 10 separate high-power fields from 1 biopsy specimen in each case; all specimens submitted to full analysis included detrusor muscle.

(i) Semiquantitative assessment. Sections were coded and subjectively quantified for the density of immunoreactive nerves observed on an arbitrary scale of 1 to 5 (1 = sparse, 5 = dense).

(ii) Quantitative assessment. Full details of the technique used have been reported previously (Gosling *et al.*, 1986). Briefly, the technique used was based on the use of an eyepiece graticule and the results were corrected as far as possible to allow for muscular hypertrophy and hyperplasia.

Biochemical assay

Pieces of tissue were stored in liquid nitrogen until peptide extraction. The bladder tissue was weighed and the peptides extracted into 0.5 M acetic acid in polypropylene tubes in a boiling water bath for 15 min. The samples were homogenised, centrifuged for 30 min at 3500 g and the supernatant was lyophilised.

VIP, SP and CGRP were quantified using an inhibition enzyme-linked immunosorbent assay as described previously (Stjernschantz *et al.*, 1982; Belai *et al.*, 1985) and the results were expressed as pmol/g tissue. Tissue was assayed in duplicate and at 2 dilutions. Control samples were always assayed at the same time as unstable obstructed bladder samples.

Table Density of VIP-, NPY-, CGRP-, SOM- and SP-immunoreactive Nerves in the Bladder Detrusor from Controls and Patients with Benign Prostate Outflow Obstruction

Group	*Patient*	*VIP*	*NPY*	*CGRP*	*SOM*	*SP*
Control	1	++++	+++++	+++	+	++
	2	++++	+++	+++	0	+
	3	+++	+++++	+++	+	+++
Stable obstructed	4	+++	++++	+	nd	+
	5	+	+++	+	nd	+
	6	++	+++++	+	0	+
	7	+++	++++	+	+	+
Unstable obstructed	8	0	+++	0	0	0
	9	0	+++	0	nd	+
	10	+	+++	0	0	0
	11	+	++++	0	nd	0
	12	+	++++	+	nd	+
	13	0	+	0	0	0
	14	+	+++	+	0	0
	15	++	++	0	0	0
	16	0	++	0	0	0
	17	0	+	0	0	0
Acute retention	18	++	++++	0	nd	0
	19	+	+	+	nd	0
	20	+	+++	+	0	0
	21	+	+++	+	0	0
	22	++	+++	0	0	0

Density of nerve fibres· +++++, very dense, +, sparse 0 = no immunoreactive nerve fibres seen; nd = not determined.

Statistical analysis

All results are expressed as mean ± SEM. Statistical analyses were only performed on the objective data to contrast patients with controls and compare results obtained in each sub-group where appropriate. In view of the nature of the subjective quantification, statistical analysis of these data was not appropriate. Although in most groups the data approximated to a normal distribution, in view of the small sample sizes, non-parametric statistical analysis was performed using a 2-tailed Mann-Whitney U test to determine statistical significance. $P \leqslant 0.05$ was considered to be significant.

Results

Histological localisation of neuropeptides

The highest density of neural immunoreactivity in the bladder was to NPY (Table). Although nerve staining for this compound was occasionally seen in the submucosal tissue, its predominant localisation was in the detrusor muscle layer. VIP was present with a similar distribution but in addition, a number of VIP-like immunoreactive nerves were present within the lamina propria. Both VIP and NPY-like immunoreactive nerve fibres were seen around blood vessels. No immunoreactive neural

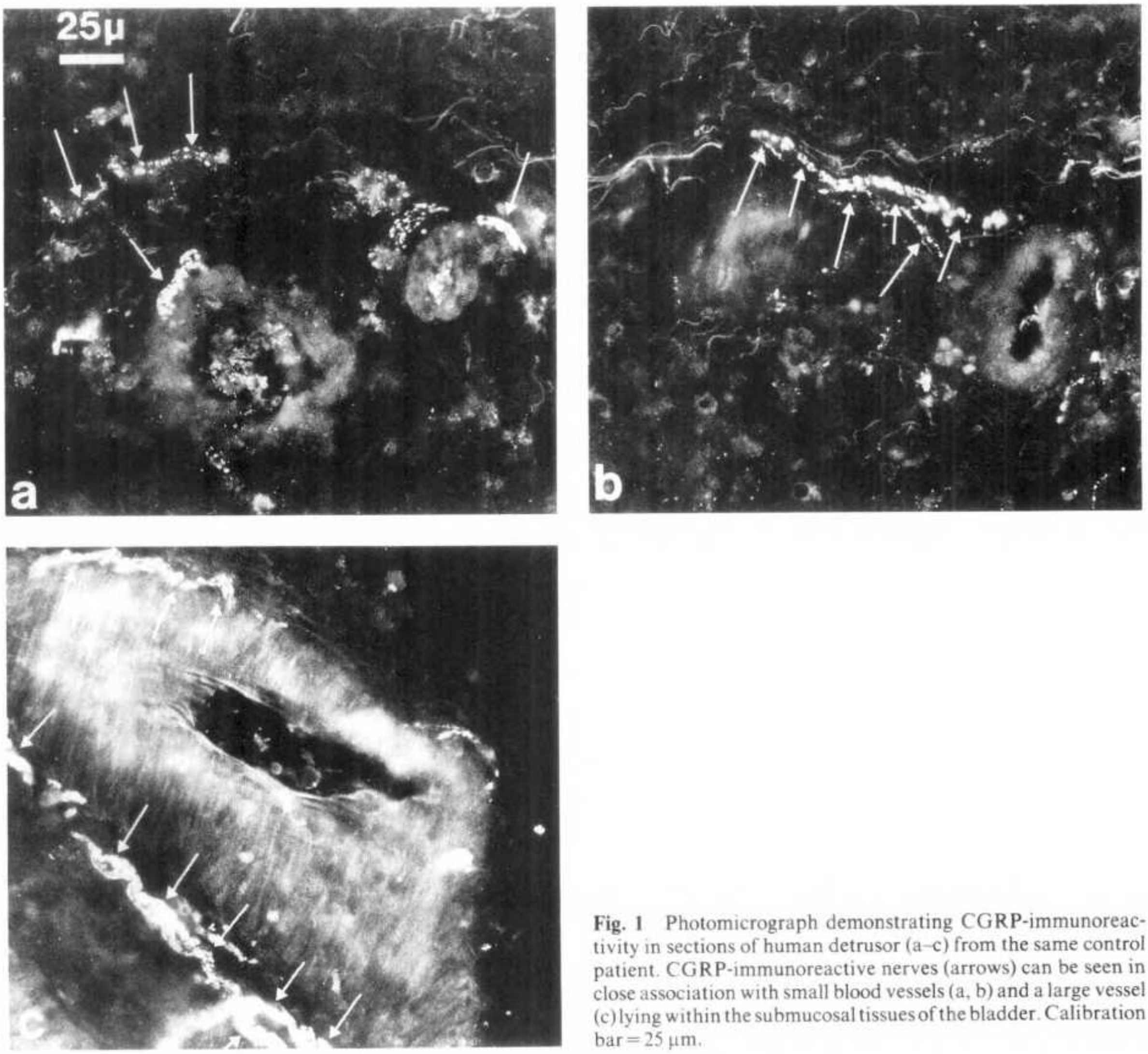

Fig. 1 Photomicrograph demonstrating CGRP-immunoreactivity in sections of human detrusor (a–c) from the same control patient. CGRP-immunoreactive nerves (arrows) can be seen in close association with small blood vessels (a, b) and a large vessel (c) lying within the submucosal tissues of the bladder. Calibration bar = 25 µm.

ganglia were identified. CGRP-like immunoreactivity was found predominantly in relation to blood vessels in the mucosa with only isolated nerve fibres being identified in detrusor muscle and submucosal tissues (Fig. 1). SP-like immunoreactive nerves, although present in a similar density to CGRP, were principally localised in the mucosa and submucosal layers. In contrast, there were very few somatostatin-like immunoreactive nerves and, when present, these were localised within the submucosal tissues.

Neural quantification

Semi-quantitative assessment of these data showed that there was a significant reduction in immunoreactivity to all of the neuropeptides in the obstructed bladder except NPY (Table). Use of a quantitative technique, with correction of the results for muscular hypertrophy and alterations in the connective tissue content of detrusor muscle (Figs 2, 3) demonstrated that the reduction in VIP-immunoreactivity in the unstable obstructed bladder was significant ($P<0.05$). CGRP and SP-immunoreactive nerves were present in the control bladder at densities of 25 ± 14 and 1 ± 1 nerves/mm^2 respectively, but were not seen in the obstructed bladder. There was less than 1 somatostatin-immunoreactive nerve per high-power microscope field in all groups.

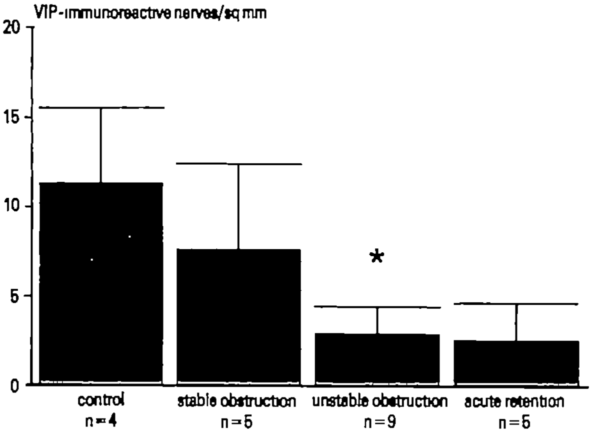

Fig. 2 Detailed results for the quantification of VIP-immunoreactive nerves in detrusor muscle from control and obstructed (stable, unstable, acute retention) bladders For each patient, 10 separate high-power fields were studied Quantitative technique. results are expressed as the mean * ± standard error of the mean Statistical analysis to contrast groups to control using a Mann-Whitney test demonstrated a significant difference for the unstable obstructed group ($P<0.05$).

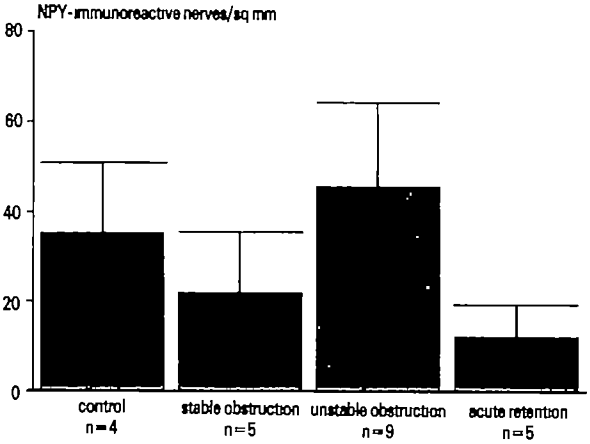

Fig. 3 Detailed results for the quantification of NPY-immunoreactive nerves in detrusor muscle from control and obstructed (stable, unstable, acute retention) bladders. For each patient, 10 separate high-power fields were studied. Quantitative technique: results are expressed as the mean ± standard error of the mean. Statistical analysis carried out to contrast groups to control using a Mann-Whitney test demonstrated no significant differences.

Biochemical assay

The amount of bladder tissue available limited the biochemical analysis to determination of VIP, SP and CGRP content (Figs 4–6). The results confirmed the presence of all 3 peptides within the bladder tissue. CGRP was present at a 10- to 15-fold lower concentration than either VIP or SP, while SP appeared to be present in a higher concentration than VIP, despite the more promi-

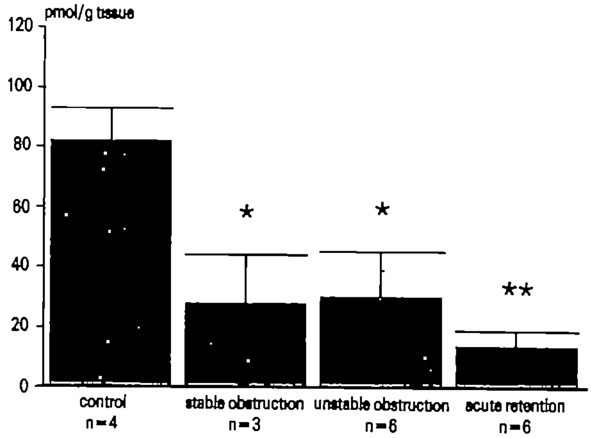

Fig. 4 Substance P content (pmol/g tissue) of control, unstable obstructed, stable obstructed and acute retention bladder. Bars represent mean ± standard error of the mean. The Mann-Whitney test was used to assess statistical significance as compared to control, ** = $P<0.02$, * = $P<0.05$

nent immunoreactivity for VIP seen on microscopy. The most striking change in neuropeptide concentration in the obstructed bladder body compared with controls was the reduction in SP content (stable and unstable obstructed, $P<0.05$; acute retention bladder, $P<0.02$) (Fig. 4). There was a tendency for VIP content to be lower in the obstructed bladder than the controls but this did not reach statistical significance (Fig. 6). CGRP levels were not significantly different in any of the tissues studied (Fig. 5).

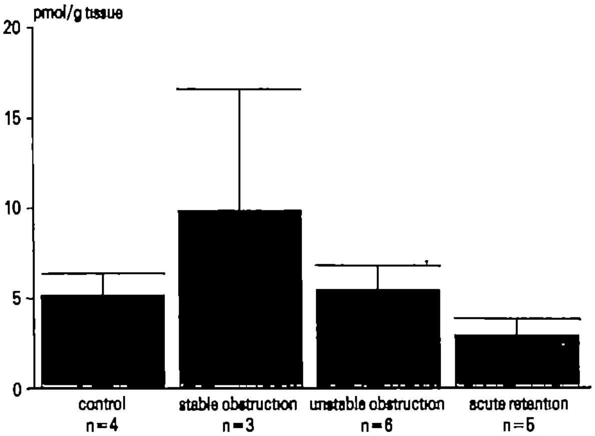

Fig. 5 Calcitonin gene-related peptide content (pmol/g tissue) of control, unstable obstructed, stable obstructed and acute retention bladder. Bars represent mean ± standard error of the mean. The Mann-Whitney test was used to assess statistical significance of the changes in obstructed groups compared with control. No statistically significant differences were evident.

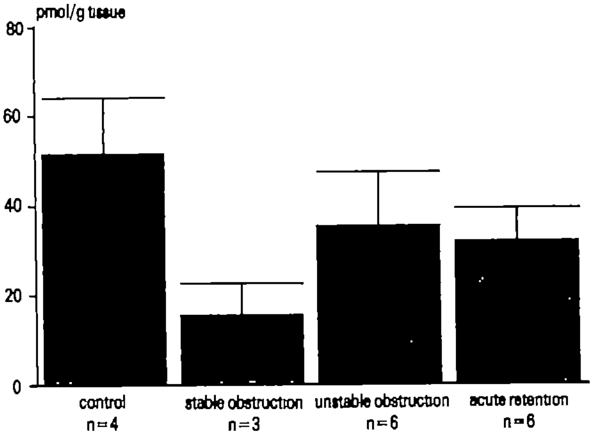

Fig. 6 Vasoactive intestinal polypeptide content (pmol/g tissue) of control, unstable obstructed, stable obstructed and acute retention bladder. Bars represent mean ± standard error of the mean. The Mann-Whitney test was used to assess statistical significance of the changes in obstructed groups compared with control. No statistically significant differences were evident.

Discussion

Despite the potential importance of neuropeptide neurotransmitter mechanisms in the function of the normal and obstructed bladder, there has been little work on the localisation of neuropeptides within the normal human bladder (Gu *et al.*, 1983a, 1984). At present, the distribution and role of peptides contained in the sensory nerves of the human bladder remain obscure. Previous studies have suggested that the sensory innervation is associated with the prominent acetylcholinesterase (AChE)-positive nerves seen within the lamina propria of the urethra and bladder (George and Dixon, 1986). In recent years it has been suggested that a number of the peptides are putative neurotransmitters within primary afferent neurons (Gibbins *et al.*, 1987), including SP (Lembeck, 1953; Nicoll *et al.*, 1980), and CGRP, somatostatin and VIP (Jancsó *et al.*, 1977; Sundler *et al.*, 1985). Although previous studies have reported an abundance of CGRP-like immunoreactivity in the rat and guinea-pig bladder, concentrated particularly in a dense submucosal neural plexus (Yokokawa *et al.*, 1986), the localisation of this peptide has only recently been documented in the human bladder (Crowe *et al.*, 1991). No previous studies have investigated the changes that occur in obstructed detrusor muscle.

In the present study we have shown that the number of VIP-containing nerve fibres and both content and number of SP-containing nerve fibres are reduced in the obstructed bladder and that SP content is particularly diminished in the acute retention bladder. These changes are unlikely to be age-related (Benson *et al.*, 1979; Gilpin *et al.*, 1986; Jungblut *et al.*, 1989) since the 4 groups studied were well matched for age. Furthermore, parallel studies of acetylcholinesterase staining on the same tissue did not demonstrate a significant age-related change (unpublished data). Tissue was obtained from the bladder dome which is known to have a uniform structure and dense innervation and comprises over 90% of the body of the bladder (Gosling *et al.*, 1983). Any changes seen are therefore likely to be relevant to the function of the whole bladder. Both quantitative and semiquantitative assessments of the innervation by SP- and CGRP-immunoreactive nerves demonstrated that the density of these nerves was substantially reduced in the obstructed bladder. Immunoassay for SP confirmed this reduction but there was no associated change in CGRP content in the obstructed bladder. These findings provide the first evidence for a disturbance of the afferent innervation of the obstructed human detrusor and are consistent with the reported reduction in SP in the obstructed rat bladder model (Andersson *et al.*, 1988).

These results illustrate that there are methodological problems associated with the quantitative assessment of innervation in a tissue such as the detrusor muscle where the neuropeptide-immunoreactivity is patchy and often sparse. This graticule-based technique tended to produce inconsistent results owing to the large and unpredictable error introduced by the effect of graticule positioning. This was reflected by the low neural count/mm^2 muscle and the high standard error of the mean for these results. This work provides validation for the continued use of semiquantitative subjective assessment in studies of neuropeptide immunoreactivity. It must be remembered that immunohistochemical assessments relate to the density of innervation in a given tissue area, whereas immunoassay data relate to the total tissue content for a substance. This may explain some of the apparent discrepancies in the data obtained.

The importance of the afferent limb of the micturition reflex has been increasingly recognised (Maggi *et al.*, 1986). A study of the rat model suggests that there is an increase in local afferent spinal reflex activity in the presence of obstruction (Steers and De Groat, 1988). Further studies have suggested that there is hypertrophy of nerves innervating the obstructed bladder (Steers *et al.*, 1989). A tempting explanation for this latter observation is that this neural hypertrophy represents a secondary phenomenon in residual nerves in response to the local detrusor denervation.

CGRP and SP have been shown by a number of workers (Yokokawa *et al.*, 1986) to co-exist within isolated nerve fibres in the lamina propria with an additional population of nerves containing either CGRP or SP (Sundler *et al.*, 1985; Yokokawa *et al.*, 1986). In the rat, application of capsaicin, which selectively degranulates unmyelinated sensory fibres, produces a profound reduction in both SP and CGRP content and results in increased bladder capacity (Maggi and Meli, 1986) and urinary retention (Sharkey *et al.*, 1983). Application of SP and related neurokinins to the mammalian bladder produces contractile effects (Erspamer *et al.*, 1981; Maggi and Meli, 1986; Dion *et al.*, 1988). However, Kalbfleisch and Daniel (1987) in studies on human bladder challenged the suggestion that these contractile motor effects represented a true physiological response, since selective SP tachyphylaxis and a SP inhibitor failed to reduce the NANC response to field stimulation.

A dramatic reduction in VIP-like immunoreactivity in the detrusor muscle of bladders exhibiting idiopathic unstable behaviour, compared with normal bladders, has been reported (Gu *et al.*, 1983b). The much smaller, yet significant reduction in VIP-immunoreactivity reported here in the unstable obstructed bladder supports the suggestion that there is a disturbance affecting the VIP-containing nerves of the bladder. The literature reveals controversy as to the pharmacological role of VIP in the human bladder; there are reports both in favour of and against VIP having a neuromodulatory role (Klarskov *et al.*, 1984, 1987; Kinder and Mundy, 1985; Kinder *et al.*, 1985; Sjögren *et al.*, 1985).

Of the peptides studied, NPY seemed least affected in the obstructed bladder. NPY is often found in sympathetic nerve fibres; however, since the sympathetic innervation of the normal human detrusor is sparse, it is unlikely that the NPY-like immunoreactivity seen here lay solely within these nerve fibres. Indeed, denervation studies conducted in the rat have identified a separate population of NPY fibres originating from cell bodies in pelvic ganglia (Mattiasson *et al.*, 1985). The distribution of both NPY- and VIP-immunoreactivity noted in this study, although supporting a principal role in the motor innervation of detrusor muscle, suggests that these 2 peptides may also participate in the regulation of blood flow within the bladder wall and may have epithelial functions. NPY occurs in high concentrations elsewhere in the male genitourinary tract (Gu *et al.*, 1983a) and is known to modulate nerve-mediated contraction and cause vasoconstriction of blood vessels (Adrian *et al.*, 1984; Lundberg *et al.*, 1985).

It is clear from this investigation that a number of putative neuropeptide transmitters occur in the human detrusor and that their concentration is reduced in the presence of obstruction. The aetiology of obstructive detrusor instability is clearly related to a more widespread disruption of the normal innervation of the human detrusor than has been previously recognised and may be particularly related to the sensory innervation. Further study of the localisation of neuropeptides and their receptors and of the pharmacological actions of these substances within the normal and obstructed human detrusor could possibly provide new therapeutic options for the control of functional disorders of the bladder.

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Is There Still a Place for Prolonged Bladder Distension?

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Summary—Over a 2-year period, 31 patients underwent prolonged hydrostatic bladder distension for benign and malignant bladder disease in this unit. Of these, 29 patients had benign functional disorders or bladder contracture, and in 2 patients hydrodistension was performed for complications of treatment for bladder neoplasia. Of the 29 patients with benign disease, 6 observed marked improvement and 8 some improvement in their symptoms, and 12 received no benefit. Patients with detrusor hypersensitivity fared better than those with detrusor instability or interstitial cystitis. A patient with malignant bladder disease died soon after the procedure as a result of a myocardial infarction. Problems attributed to the hydrostatic balloon catheter were responsible for 2 failures. The regional anaesthetic technique failed to provide adequate anaesthesia for hydrodistension in 9 procedures and limited the duration to 2 h in 13 others. Following recall of the perished balloon catheters by the manufacturer, and the introduction of continuous spinal anaesthesia, the number of technical failures has been reduced. This technique still has an important role to play in the relief of severe symptoms unresponsive to medical treatment, but it is important that ideal conditions are provided for hydrodistension in order to ensure maximum success, particularly when the alternative is major surgery.

The management of patients with symptoms of frequency, urgency and urge incontinence of urine remains a common problem. Therapeutic options include medical management (Abrams, 1988), transvesical injection of phenol (Blackford *et al.*, 1984), presacral selective sacral neurectomy (Lucas *et al.*, 1988), prolonged bladder distension (Dunn *et al.*, 1974), bladder transection (Hindmarsh *et al.*, 1977) and enterocytoplasty (Bramble, 1982). Prolonged bladder distension was first introduced by Helmstein (1972) for the treatment of bladder cancer, and has been subsequently popularised for the management of benign disease with encouraging long-term results (Ramsden *et al.*, 1976). The exact mechanism by which prolonged distension works remains unclear. It has been proposed that the distension may produce ischaemic or physical damage of the mucosa, nervous tissue or detrusor muscle (Dunn *et al.*, 1974).

The problems associated with prolonged bladder distension and the outcome of patients treated over a 2-year period are presented. Recently we have been using continuous spinal anaesthesia for these procedures; our experience with the technique is described and discussed.

Patients and Methods

During a 2-year period (1989–1990), 31 patients (21 women, 10 men) with a mean age 52 years (range 18–76) were treated by prolonged bladder distension (Table 1). One patient had severe frequency and urgency following instillation of Bacillus Calmette-Guérin (BCG) for carcinoma *in situ* of the bladder and another had haematuria from widespread superficial bladder carcinoma uncontrolled by endoscopic resection. The remaining 29 patients suffered from benign conditions (15 detrusor hypersensitivity, 6 detrusor instability, 6 interstitial cystitis, 2 iatrogenic disease) associated with severe irritative symptoms (frequency, nocturia, urgency and occasionally urge incontinence), and pain in the patients with interstitial cystitis. Prolonged bladder distension was used after failure of treat-

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ment with anticholinergic drugs or other medical measures. Three patients (2 with detrusor hypersensitivity and 1 with interstitial cystitis) had previously undergone prolonged distension with some benefit.

Hydrodistension technique

Two patients underwent 2 separate hydrodistensions; 37 anaesthetic procedures were required for 31 hydrodistensions. The patients were catheterised with a 12F Foley catheter prior to insertion of a 16F hydrodistension catheter (Rusch UK Ltd). Continuous hydrodistension was planned for approximately 3 h in all patients receiving regional anaesthesia. The volume of saline within the balloon was determined by gravity, but was not allowed to exceed 1 L. The height of the saline was fixed at a level of 1 m above the patient's umbilicus. Initial experience of trying to control the intravesical pressure as described by Ramsden *et al.* (1976) proved complicated and was abandoned for the above method. Following the period of distension, the balloon was deflated and the hydrodistension catheter replaced with a 16F Foley catheter left on free drainage overnight and removed the following morning.

Anaesthetic techniques

In all but 1 case a regional anaesthetic technique was attempted primarily (Table 2). In this patient, general anaesthesia had already been administered for the purpose of cystoscopy before the decision was made to perform hydrostatic distension of an hour-glass deformity following previous caecocystoplasty. In 1 patient, 2 epidurals had failed to provide adequate anaesthesia and general anaesthesia was therefore used. The remaining patients received either single dose spinal (15) or epidural anaesthesia (20) via a catheter with either bolus doses or a continuous infusion.

Results

The outcome for patients undergoing prolonged bladder distension can be seen in Table 1. In 2 patients the hydrostatic balloon catheter failed to distend and the procedure was abandoned. Three patients had previously undergone prolonged bladder distension; 1 patient with interstitial cystitis received benefit from further distension but the other 2 patients with detrusor hypersensitivity obtained no symptomatic benefit from further bladder distension (1 underwent 2 separate procedures). Another patient with detrusor hypersensitivity underwent 2 separate distensions before symptomatic benefit was achieved. Overall, for those patients with benign disease, 6 (21%) have had marked continued benefit from the treatment, 8 (28%) have experienced some improvement in their symptoms, and 12 (41%) received no benefit from the procedure. A further 2 patients have been lost to follow-up.

The patient who had previously received intravesical BCG for carcinoma *in situ* and subsequently developed severe irritative symptoms, developed haemorrhage around the hydrodistension catheter and the procedure was abandoned. The patient with widespread superficial disease developed acute cardiovascular complications during hydrodistension, culminating in a myocardial infarction from which he died.

Subsequent procedures

Seven of the 12 patients with benign conditions who failed to benefit from hydrostatic distension have subsequently proceeded to surgery. A further 6 have undergone ileocystoplasty and 1 prostatectomy (destrusor instability was considered secondary to bladder outflow obstruction). Two patients with interstitial cystitis and 1 with post-radiotherapy cystitis have undergone repeat hydrodistension

Table 1 Indications for Prolonged Bladder Distension and the Early Results

Aetiology (no of patients)	*Response*			*Procedure abandoned*	*Lost to follow-up*	*Comment*
	Good	*Fair*	*Poor*			
Detrusor hypersensitivity (15)	4	4	6		1	2 patients, 2 distensions
Detrusor instability (6)		2	3		1	
Interstitial cystitis (6)	2	1	2	1		Balloon failure
Bladder carcinoma (1)				1		Myocardial infarction
Post-caecocystoplasty (1)		1				
Post-BCG (1)				1		Haemorrhage
Post-DXT (1)				1		Balloon failure

Table 2 Anaesthetic Techniques

Anaesthetic technique (no.)	*Anaesthetic result*			*Failed distension*	*Mean distension time (min)**	*Complications (no.)*
	Good	*Partial*	*Failed*			
Epidural (20)	12	2	4	2	184	Dural puncture (1) Hypotension** (5)
Spinal (15)	13	1	1		119	Hypotension** (4)
General (2)	2				20	None

* Only relates to procedures with good anaesthetic result
** Hypotension requiring treatment with vasopressors

during cystoscopy under general anaesthesia with some benefit. The patient with severe irritative symptoms following BCG therapy has had spontaneous resolution of his symptoms.

Discussion

Outcome

The results of prolonged bladder distension for functional bladder disturbance have to be seen in the context of the alternatives available. Ileocystoplasty is associated with occasional mortality and significant morbidity, *e.g.* difficulty in emptying the bladder; this may require clean intermittent self-catheterisation (Bramble, 1990) and there may be an increased risk of malignancy. Many urologists would subject patients with an essentially benign condition to such major surgery only after all alternatives had been exhausted, even if these procedures have a relatively low success rate. Prolonged bladder distension is one of these alternatives; it is simple and associated with a low morbidity rate. Symptomatic relief was achieved in approximately 49% of patients undergoing this procedure in this series. Possible reasons for failure in the remaining 51% will be considered separately.

Hydrodistension technique

The ideal duration of distension and the volume required for each condition and each patient remain uncertain. Initial reports recommended intermittent distension (Dunn *et al.*, 1974) but subsequent series have used continued distension with varying success (Pengelly *et al.*, 1978; Wolk and Bishop, 1981). It has been our intention to use continuous distension for 3 h (provided anaesthesia is adequate), but there is no recognised standard distension time and some have used distension for up to 6 h (Wolk and Bishop, 1981). It is possible that 3 h are insufficient and some patients may require more than one procedure before benefit is achieved.

Case selection

Another possible reason for poor response is case selection. From this series it appears that patients with detrusor hypersensitivity and those with interstitial cystitis are more likely to respond than are patients with detrusor instability. There is no way of predicting the likelihood of success in each individual patient and so it is our policy to offer this form of treatment to all patients in whom major surgery is considered. The only fatality in this series was a patient who was regarded as unfit for cystectomy; hydrodistension was considered the only feasible means of controlling the haemorrhage from his widespread superficial disease.

Balloon failure

It became apparent that technical faults were sometimes responsible for failure of the procedure, as in 2 cases where the hydrodistension catheter burst. Several other catheters were found to have perished. The manufacturer (Rusch UK Ltd) has recalled all hydrodistension catheters, acknowledging a fault in the production which resulted in premature perishing of the balloon. The new catheters have stronger balloons. We used to monitor the intravesical pressure routinely (Ramsden *et al.*, 1976), but found it increasingly difficult to correlate the measured pressure with the distension. Testing the balloons confirmed that considerable pressure was necessary simply to overcome the tension of the balloon wall, and this made it impossible to relate measured pressure to pressure within the active bladder. It may be that we are distending the bladder at too low a pressure for adequate results. The design of the balloons, incorporating a balance between strength and distensibility, could probably be improved.

Anaesthetic problems

It was apparent that the anaesthetic techniques may have contributed significantly to failure of the procedure, either because of inadequate anaesthesia to permit distension or by limiting distension time. The distension time for both procedures under general anaesthesia was 20 min, with volumes of 220 and 500 ml respectively. Lasting symptomatic benefit from this procedure was experienced by 1 patient. The duration of hydrostatic distension was limited by the onset of pain in all patients who received single dose spinal anaesthesia, with a mean distension time for the 13 successful blocks of 2 h and with a mean distension volume of 592 ml (range 350–800). One spinal anaesthetic gave only a partial block and another failed completely; in both instances anaesthesia was considered inadequate for hydrodistension. Hypotension requiring vasopressor treatment was required for 4 patients during spinal anaesthesia. Epidural anaesthesia was used for 20 procedures and provided adequate anaesthesia for 12, with a mean hydrodistension time of 184 min and a mean distension volume of 562 ml for the successful blocks (range 300–1000). Failure to insert the epidural catheter or asymmetry of anaesthesia prevented adequate bladder distension in 4 patients and limited the duration of distension in 2. Hypotension requiring vasopressor treatment was required for 5 patients during epidural anaesthesia.

Continuous spinal anaesthesia

Following discussion with our anaesthetic colleagues, it was considered that the anaesthetic requirements for this procedure would be best provided by continuous spinal anaesthesia. This method of regional anaesthesia has received renewed interest following improvements in product development, permitting a microspinal technique (Hurley and Lambert, 1987). Continuous spinal anaesthesia is useful for prolonged procedures, providing a reliable dense symmetrical block and permitting titration of anaesthesia with relatively small doses of local anaesthetic agent, with no increase in complications over single-dose spinal anaesthesia (Denny *et al.*, 1987). To date, 14 patients have undergone prolonged bladder distension under continuous spinal anaesthesia using the 28G CoSpan spinal catheter via a standard 22G spinal needle (The Kendall Company). In each case the technique provided suitable conditions for 3 hours hydrodistension. One patient required treatment with vasopressors for hypotension following the first dose of bupivacaine. One patient developed a mild headache associated with an upper respiratory tract infection following continuous spinal anaesthesia. This was not considered typical of post-dural puncture headache and it settled spontaneously. Another patient received a single dose spinal anaesthetic because introduction of the spinal catheter proved impossible. He subsequently developed a post-dural puncture headache, requiring an epidural blood patch.

We advocate prolonged hydrostatic balloon distension of the bladder in all patients where the alternative is major surgery. Even under ideal conditions the procedure will fail to provide symptomatic benefit in some patients. In order to provide optimum conditions for success we recommend continuous spinal anaesthesia. It is too early to assess the clinical outcome of prolonged distension in this group of patients, but initial results look favourable. We also recommend that all old stocks of hydrodistension catheters should be returned to the manufacturers for replacement by new ones free of charge.

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Botulinum Toxin in the Treatment of Chronic Urinary Retention in Women

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Summary—Six women were identified as having difficulty in voiding or complete urinary retention due to abnormal myotonic-like electromyographic (EMG) activity in the striated muscle of the urethral sphincter. An attempt was made to improve voiding by injection of botulinum toxin into the striated sphincter muscle. Although 3 patients then developed transient stress incontinence, demonstrating that sufficient botulinum toxin had been given to cause sphincter weakness, no patient had significant symptomatic benefit.

Fowler and Kirby (1985) reported profuse, abnormal EMG activity in the striated urethral sphincter muscle in 5 women who were in complete urinary retention. At first, this activity was thought to be a form of "pseudomyotonia", but detailed examination of the activity, recorded using a single fibre needle electrode, showed that it consisted of repetitive firing of complex potentials. The decelerating component of parts of these EMG complexes gave the activity its myotonic-like sound and they were called "decelerating bursts" (Fowler *et al.*, 1985).

Prior to this finding of abnormal EMG activity, urinary retention in women was widely thought to be either hysterical or psychogenic (Larsen *et al.*, 1963; Margolis, 1965; Allen, 1972; Krane and Siroky, 1979; Bassi *et al.*, 1988). It is easy to understand how such a misapprehension might arise: these women are otherwise neurologically intact and the EMG abnormality is highly localised and occasionally elusive even within the urethral sphincter. Other neurophysiological investigations of the pelvic floor are normal. This type of EMG activity can be recorded from the urethral sphincter in cases of disturbed bladder function other than urinary retention (Butler, 1978; Dyro *et al.*, 1983; Fowler *et al.*, 1988) it is however the commonest EMG finding in young women with isolated urinary retention (Fowler, in preparation). Nevertheless, a proportion of women with retention have a normal sphincter EMG and the cause of their retention remains unexplained.

There is currently no effective treatment for the abnormal EMG activity. Most patients undergo urethral dilatation at some stage but this offers only temporary relief and the majority have to be taught clean intermittent self-catheterisation. What is required is some way of abolishing the myotonic-like EMG activity and improving urethral relaxation. In an attempt to achieve this we injected botulinum toxin into the striated muscle of the urethral sphincter.

Patients and Methods

Six women gave informed consent to injection of the toxin: 2 were in complete urinary retention and 4 had intermittent retention with intercurrent symptoms of voiding difficulty (Table). All had been shown by earlier needle electrode studies to have the characteristic pattern of EMG activity, *i.e.* profuse, spontaneous, complex repetitive discharges and decelerating bursts.

The correct site for injection of the sphincter was found using EMG monitoring. A hollow cannula electrode (CH Electrodes, Bromley, UK) was

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Table Details of Patients and their Response to Urethral Sphincter Injection of Botulinum Toxin

Case no	*Age (years)*	*Urinary symptoms*	*Result of injection*
1(MS)	45	Complete urinary retention	Stress incontinence for 10 days
2(LF)	45	Complete urinary retention	Stress incontinence for 10 days
3(MO)	25	Intermittent retention. Difficulty in voiding	No change
4(TC)	25	Intermittent retention. Difficulty in voiding.	No change
5(CM)	33	Intermittent retention Difficulty in voiding	No change
6(JG)	28	Intermittent retention Difficulty in voiding	Stress incontinence. Easier to self-catheterise for 10 weeks

connected so that the EMG could be recorded from the tip and the injection then be made at the recording site (Fig.).

Botulinum toxin type A (supplied by the Division of Biologics, Porton Down, Salisbury, UK) was used. This has a biological activity of 2000 mouse units in 0.05 μg of toxin-haemagglutin complex.

Five patients received a single dose of 0.005 μg (200 mouse units) of botulinum toxin: 1 patient received 2 injections of 0.0025 μg separated by an interval of 2 weeks. The injection was given into one side of the sphincter to minimise the number of needle punctures.

Results

The response to treatment is shown in the Table. Both women who had been in complete retention passed urine *per urethram* for the first time in many months. However, this urine loss was in the form of stress incontinence, which they considered unacceptable, and the ability to co-ordinate a normal micturition reflex was not restored. Of the 4 women still able to void with difficulty, 3 noticed no change. One reported a minor degree of stress incontinence but noted also that it was easier to perform self-catheterisation. The stress incontinence resolved within the following month and the difficulty in performing self-catheterisation returned after 11 weeks.

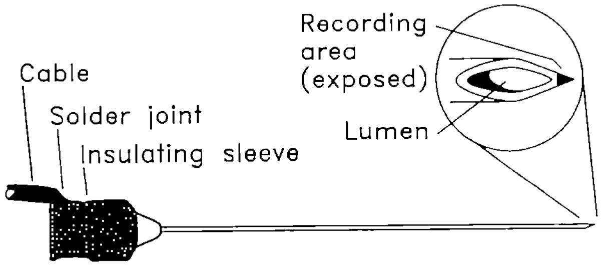

Fig. Diagram of hollow cannula EMG electrode (drawn by C. Hogg, CH Electrodes)

Discussion

Correction of disordered function by injection of botulinum toxin type A in an overactive muscle was first introduced for the treatment of strabismus by Scott (1981). Botulinum toxin injection for the treatment of dystonic disorders is now well established and is successfully used in the treatment of spasmodic torticollis (Stell *et al.*, 1988; Blackie and Lees, 1990), blepharospasm and dystonic dysphonia (Jankovic *et al.*, 1990). Botulinum toxin has also been used in the pelvic floor to treat anismus, a condition regarded as a form of focal dystonia (Hallan *et al.*, 1988; Mathers *et al.*, 1988). The only other use of botulinum toxin A injection into the striated muscle of the urethral sphincter has been for the treatment of detrusor-sphincter dyssynergia in spinal cord injury patients (Dykstra *et al.*, 1988).

The suggestion that complex repetitive discharges in the urethral sphincter are due to spread of ephaptic excitation between muscle fibres was made by Dyro *et al.* (1983) and is supported by our own single fibre EMG studies which demonstrated very low jitter values between parts of the complexes (Fowler *et al.*, 1985). If this is the case, neuromuscular transmission is important only in initiating the abnormal activity, and the failure of botulinum toxin to correct it might be expected.

We have previously reported an association between the abnormal EMG activity and polycystic ovaries (Fowler *et al.*, 1988) and although this association may provide some indication of possible future therapeutic approaches, the underlying mechanism remains uncertain.

In summary, our experience has shown that botulinum toxin does not have a beneficial effect in women whose urinary symptoms result from impaired urethral sphincter relaxation due to complex repetitive discharge activity. The finding that 3 women developed transient stress incontinence following the injection is evidence that sufficient botulinum toxin had been given to weaken the striated sphincter muscle. This observation lends further weight to the hypothesis that the abnormal activity of the sphincter muscle is due to ephaptic transmission of impulses between muscle fibres and is not the result of repetitive firing of reinnervated motor units.

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Effect of Substance P on Detrusor Muscle in Rats with Diabetic Cystopathy

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Summary—Diabetic cystopathy (DCP) is a well known complication in diabetes mellitus (DM). In the present experimental study, DM was induced in rats by streptozotocin and DCP was confirmed on cystometry.

In vitro studies on detrusor strips from diabetic rats showed an increased contractile response to substance P (SP) compared with controls, indicating denervation supersensitivity. A decreased response to capsaicin in diabetic detrusor strips indicated a decreased neuronal content of SP or a diminished number of SP-containing sensory nerves. This suggests that DM induces alterations in nerves containing SP which may be at least partly responsible for sensory loss and the development of DCP.

Vesical dysfunction is a common but little studied complication of diabetes mellitus (DM) (Frimodt-Møller, 1976). The prevalence varies from 27 to 85% among unselected diabetics (Buck *et al.*, 1974; Norlén *et al.*, 1983a) and is higher in juvenile diabetes (Faerman *et al.*, 1971). The term "diabetic cystopathy" (DCP) was coined by Frimodt-Møller (1976) to describe a syndrome with infrequent voiding, a feeling of incomplete emptying, straining and weak stream. Urodynamic investigation reveals decreased bladder sensibility, increased bladder capacity, decreased detrusor contractility, decreased urinary flow rate and residual urine. Much evidence supports the theory that DCP is a manifestation of diabetic neuropathy with a loss of sensation as the primary defect (Motzkin, 1968; Buck *et al.*, 1974).

One of the most important neurotransmitters in the afferent nervous system is substance P (SP) (Hökfeldt *et al.*, 1975). In an experimental study of rats with streptozotocin-induced DM and urodynamic findings resembling DCP, a diminished amount of detectable substance P-like immunoreactivity (SPLI) was found in the detrusor (Dahlstrand *et al.*, 1988). Previous studies have shown that SP also has a contractile effect on the detrusor of rats and other species (Sjögren *et al.*, 1982; Norlén *et al.*, 1983b; Berggren *et al.*, 1988).

The aim of the present *in vitro* study was to investigate whether the observed reduction of SPLI in the detrusor in rats with DM was accompanied by a change in the effect of SP on spontaneous motility in isolated detrusor strips. For this purpose capsaicin, a drug which affects thin unmyelinated afferent C-fibres and releases the neurotransmitters, was also used. It has been shown that capsaicin-induced contraction in the ileum is mediated by release of SP (Barto *et al.*, 1982).

Materials and Methods

Induction of diabetes

Eighteen female Sprague-Dawley rats with an initial body weight (bw) of approximately 200 g were included in the study. To induce DM, streptozotocin dissolved in saline was administered intraperitoneally (65 mg/kg bw). Control rats received saline intraperitoneally. All rats were kept under identical conditions for 8 weeks with free

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access to food and water. Failure to gain weight, glucosuria and raised blood glucose were regarded as signs of manifest DM.

Cystometry

To ascertain whether urodynamic changes resembling DCP were present, cystometry was performed 8 weeks after induction of diabetes. The rats were anaesthetised with pentobarbitone sodium 50 mg/kg bw intraperitoneally. A thin catheter (Venflon 0.3 mm) was introduced through the urethra into the bladder, connected to a T-tube which was linked to a Statham pressure transducer (P23 DC), and an infusion of saline (37°C) was given at a rate of 0.3 ml/min. The intravesical pressure was registered on a Grass polygraph. When the rats started to micturate along the catheter, the infusion was stopped and the catheter withdrawn. When micturition ceased, the catheter was reinserted and residual urine measured. The volume infused when micturition began was considered to represent the bladder capacity.

In vitro studies

The rats were sacrificed and the abdomen was opened via a midline incision. The bladder was removed and dissected free from connective tissue and fat before being weighed. Detrusor strips approximately 10 mm long and 1 mm wide were prepared from the bladder dome and mounted in an 8-ml mantled organ bath (temperature 37°C) containing Krebs solution (composition in mmol per litre: NaCl 122, KCl 4.73, CaCl 2.49, $MgCl_2$ 1.19, $NaHCO_3$ 15.5, KH_2PO_4 1.19 and glucose 11.5). The solution was bubbled continuously with 96% O_2 and 4% CO_2, giving a pH of 7.4. One end of each preparation was connected to a muscle holder and the other via a silk thread to a Statham FT 03 force transducer. The isometric force was recorded on a Grass polygraph. Preparations were stretched with a preload of 500 dyn. After a 30-min stabilisation period, the baseline was determined by adding calcium-free Krebs solution. The preparations were again allowed to stabilise for 30 min after changing to normal Krebs solution and drugs were administered in graded doses. SP and capsaicin (Sigma Chemicals, USA) were added to give a final concentration of 10^{-10}–10^{-7} in the bath. Finally, the preparations were exposed to high K^+ solution (same composition as above except that 122 mmol Na^+ was changed to K^+). The preparations were exposed to calcium-free Krebs solution again to ensure that the baseline remained unchanged. Between each administration of the various drugs and doses, or change in the composition of Krebs solution, thorough rinsing was performed with ordinary Krebs solution.

The phasic activity was quantified by calculating the area below the registration of the mechanical activity with an electronic plotter. The effects of the drugs were calculated as the ratio between the integrated area during 2 min after exposure and the integrated area during 2 min immediately before exposure. The response curves and ED_{50} values were calculated for each tissue strip from a series of exposures to different concentrations.

Statistics

Results are expressed as mean ± SEM and Student's *t*-test was used for comparison of the data. $P \leq 0.05$ was considered significant.

Results

After 8 weeks, 7/10 rats injected intraperitoneally with streptozotocin had a blood glucose level >15 mmol, glucosuria and had ceased to gain weight, indicating manifest DM. The mean body weight in the diabetic rats was 202 ± 5.7 g, compared with 270 ± 3.2 g in control animals ($P<0.001$). The bladder weight was increased in diabetic rats compared with control rats; 0.182 ± 0.013 g and 0.102 ± 0.005 g respectively ($P<0.002$). The rats injected with streptozotocin that had not developed diabetes were not used. None of the control animals had raised blood glucose or glucosuria.

Cystometry

On cystometry it was found that the diabetic animals had a pattern different from that of the control animals. During the filling phase, control rats had spontaneous contractions of the detrusor, which was not recorded in rats with DCP (Fig. 1). In the diabetic animals the intravesical pressure increased slowly until micturition started. In control rats there was a sudden sharp rise in pressure before micturition. Cystometric bladder capacity in control animals was 1.1 ± 0.05 ml and in diabetic animals 2.9 ± 0.06 ml ($P<0.0001$). No significant difference in micturition pressure was recorded between the groups. One control rat had a residual urine of 0.2 ml but the others had none. All diabetic rats had residual urine (mean value 0.9 ± 0.14 ml).

In vitro studies

The spontaneous motility was slightly but not significantly increased in detrusor strips from

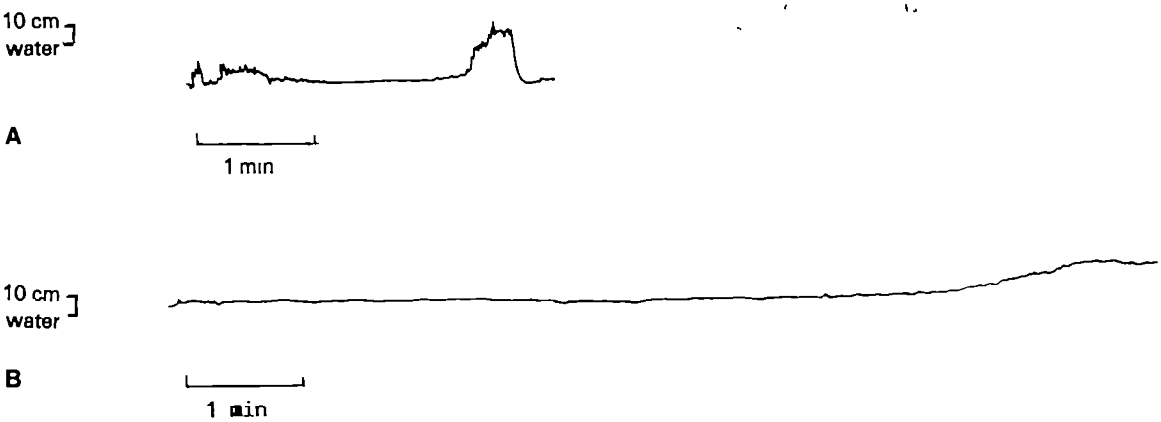

Fig. 1 (A) Bladder pressure in a control animal during infusion of saline at 0.3 ml/min Some spontaneous contractions in the detrusor are seen. After about 3 min there is a sharp rise in the intravesical pressure and a contraction of the detrusor and micturition starts. (B) Bladder pressure in a diabetic animal during infusion of saline at 0.3 ml/min. There are no spontaneous contractions; the pressure in the bladder increases slowly and micturition starts after about 6 min

diabetic rats. The strips responded with a dose-dependent contraction when exposed to graded doses of SP. Strips from diabetic rats contracted more than strips from control animals for every dose given. The responses were significantly different for the 2 higher doses (Fig. 2). ED_{50} for substance P in control rats was 1.31×10^{-8}M, in diabetic rats 0.39×10^{-8} M ($P<0.05$). The maximum contraction obtained after SP was greater in diabetic rats than in control animals.

When exposed to capsaicin 10^{-8} M, the contraction of the strips from diabetic rats did not differ significantly from that in strips from control rats.

The maximum contractile force of detrusor strips elicited by KCl was equal in the 2 groups.

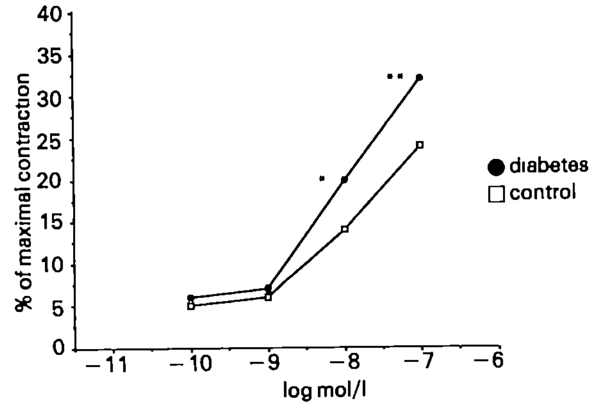

Fig. 2 Increased sensibility of strips from diabetic bladders Mean value of 7 animals. $*P<0.05$, $**P<0.01$.

Discussion

In this study, intraperitoneal streptozotocin was used to induce DM in rats. The induction was successful in 7/10 rats, which is in the same range as in previous studies (Belai *et al.*, 1985).

After 8 weeks of diabetes, the bladder wet weight was increased compared with controls. The finding of increased bladder wet weight after different experimental manipulations in rats has been reported following total denervation (Ekström and Uvelius, 1981), selective sensory denervation with capsaicin (mainly substance P fibres affected) (Sharkey *et al.*, 1983), induction of diabetes (Moss *et al.*, 1987), polyuria alone induced by sucrose in the drinking water (Carpenter, 1983) and bladder outlet obstruction (Mattiasson *et al.*, 1982). In the present study, the increased bladder wet weight came with induction of DM, a disease known to cause polyuria and sensory denervation.

The increased bladder capacity may be due to an adaptation to polyuria and/or the diabetes itself (Carpenter, 1983). It may also be due to denervation (Ekström and Uvelius, 1981; Sharkey *et al.*, 1983). The fact that diabetic bladders require a greater filling volume than normal bladders to evoke a micturition reflex may be due to decreased sensitivity. This suggestion is further supported by Steers *et al.* (1990), who studied a similar rat model and concluded that the changes may reflect alterations in the afferent limb of the micturition reflex.

During the filling phase of cystometry we found no spontaneous contraction in the diabetic bladders; the pressure increased slowly until micturition started. There was no sharp rise in pressure before micturition, as in normal bladders. This was in accordance with the findings of Moss *et al.* (1987). There was no significant difference in intravesical pressure at the onset of micturition between the 2 groups, as confirmed by Andersson *et al.* (1988).

The finding of increased residual urine in diabetic bladders has also been reported by Carpenter (1983).

In the *in vitro* studies, a slight increase in spontaneous activity in the detrusor strips from diabetic rats was recorded. This was in accordance with the finding by Moss *et al.* (1987).

In the present study, the effect of SP on spontaneous motility in isolated detrusor strips was different in diabetic and control animals. The strips from diabetic rats responded with a more powerful contraction at each dose given. A possible explanation may lie in the development of denervation supersensitivity. This supersensitivity may be specific, since Lincoln *et al.* (1986) noted no change in sensitivity to acetylcholine, noradrenaline or cholinergic nerve stimulation in a similar model. The finding of a less easily elicited micturition reflex, together with the proposed denervation supersensitivity for a transmitter known to transmit afferent impulses, indicates that diabetes induces damage to the sensory nerve system in the bladder.

Contraction of detrusor strips elicited by capsaicin was not more powerful in the diabetic group. This lends further support to the view that there is a diminished amount of SP in the diabetic bladders, since the strips from diabetic bladders were more sensitive to SP and an equal amount of released SP would have elicited a more powerful contraction in the diabetic animals than in control animals. This finding is supported by immunohistochemical (Dahlstrand *et al.*, 1988) and radioimmunoassay findings (Dahlstrand *et al.*, unpublished observations) which confirmed a significantly diminished amount of SP in diabetic bladders.

We found no change in the maximum response to KCl, although others have reported decreased sensitivity (Longhurst and Belis, 1986). Our finding suggests that there is no change in the contractility of the muscle in the detrusor.

In conclusion, 8 weeks after induction of DM in rats, urodynamic measurements confirmed DCP. *In vitro* studies on diabetic detrusor strips showed an increased contractile response to SP, indicating denervation supersensitivity and decreased response to capsaicin, in turn indicating either a decreased neuronal content of SP or a diminished number of SP-containing sensory nerves. The findings suggest that DM induces alterations to nerves containing SP and those may be at least partially responsible for sensory loss and the development of DCP.

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The Open Access Continence Resource Centre for Greater Glasgow Health Board

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Summary—The development of an open access Continence Resource Centre is described. The role of the Centre in helping the sufferers and carers is highlighted. The educational role exceeded expectations. The benefits of the centre in education, research and potential cost saving are discussed. The aims and achievements are in accord with the Department of Health document "An Agenda for Action on Continence". From its opening in August 1989 to the end of February 1992 the centre has served 8070 incontinent individuals and 4736 carers. At a cost of £44,000 per annum this represents good value for money.

Urinary incontinence is a devastating problem with distressing personal and social consequences for the sufferer. The subject in the past has not received sufficient prominence in the education of medical, nursing and paramedical staff. The demand for help by the incontinent has been restricted, firstly due to the embarrassment which is still associated with incontinence and secondly to a lack of knowledge of the range of treatment available. Only 1 in 10 individuals with urinary incontinence actually seeks help (Thomas *et al.*, 1980). In an attempt to tackle these difficulties an open access Continence Resource Centre for the Greater Glasgow Health Board Area was set up at the Southern General Hospital. Initially a pilot project, the centre has now obtained permanent status. To date, 1045 sufferers have attended and 1746 have telephoned the department; 3290 professionals have received training. The Area Committee of general practitioners approved the project.

Materials and Methods

The pilot year commenced in July 1989. Staffing was completed by September of that year. Current staffing consists of 3 sisters, 2 of whom have job-sharing contracts, giving a total of 2 whole-time equivalents, and a part-time secretary. For ethical considerations the urologists at the Southern General Hospital have no direct contact with individuals contacting the centre, although they are available to give advice on any problems the sister specialists may encounter. There is no direct mode of referral from the centre to the urology department. The specialist sisters offer to communicate with the appropriate general practitioner and nearly all of those attending agree to this. The aims of the centre are summarised in Table 1.

Table 1 Functions of the Continence Resource Centre

1	Help, advice and screening for the incontinent individual
2.	Assistance to and education of carers, professional and lay
3.	Audit of the nature and level of demand for the Resource Centre
4	Research into continence and related factors

Help, advice and screening for incontinent individuals

The centre provides a 24-h telephone advisory service. There is a direct line to the centre which bypasses the hospital switchboard. When no-one is available to take a call an answering machine records messages and contact is made as soon as

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possible, usually the next day. All are offered the opportunity to attend in person but if housebound or in some way inhibited about attending, can receive extensive advice by telephone.

The centre provides open access. Individuals may attend at any time for assessment and help with or without an appointment. The specialist nurses take a full continence history and make a nursing assessment of the problem. To aid them in their assessment they have access to a computerised history-taking program. This is a modification of work carried out previously in the urology department at the Southern General Hospital (Glen *et al.*, 1989; Morrison *et al.*, 1991). The program has been specially tailored to meet the needs of the Resource Centre (Glen *et al.*, 1991). When the history is complete the patient receives a printout with computer-generated advice. The sister will then review and discuss the printout and validate the advice as appropriate. The Figure shows an example of a complete computer printout. The history may highlight problems requiring fuller investigation, for example haematuria or infection. In these cases the patient is advised to consult his/her general practitioner for appropriate follow-up and if necessary hospital referral. An explanatory paragraph appears on all computer printouts.

Figure

Name: Bo Beep. Unit No 121212.
GP: Dr Foster.

DOB: 12/12/45. Address: 10 Cockleshell Lane.
Marital Status: s. Occupation: Shepherdess. Age: 45.

Self referral to Continence Resource Centre. Main symptom mentioned is Incontinence

Bladder function history

Patient does not think that urinary infections have occurred. Leaks at least once every 24 hours. At worst leakage is moderate. Gets wet by day only. Continence problem has moderate effect on life. Patient has had moderate stress incontinence, occurring occasionally for 6–12 months. Has had mild urge incontinence, occurring all the time for 6–12 months. Has had a feeling of incomplete voiding, leaving an amount which is small occurring occasionally for 6–12 months. Encores. Frequency which is 1–2 hourly No nocturia. Bladder problem affected by childbirth, intercourse. Symptoms made worse by alcohol Post menopausal. Does not have glaucoma. Has no neurological condition Has had no urological operations to note.

General Health

No known allergy to contrast medium No allergy to medicine. No other allergy recorded. Is on no medication. No other hospital treatment remembered. Patient has 2 children.

Computer Suggested Investigations

Urodynamics may be indicated

Reasons for Urodynamics: stress incontinence, and wants it investigated.

Computer Generated Advice

Patient to have double and regular voiding advice. [ ]
Patient to be given pelvic floor exercises. [ ]
Patient to be advised about alcohol intake and bladder [ ]

Patient may require vaginal examination

Dear Dr Foster

Your patient has attended our self referral Incontinence Resource Centre and completed a computerised history taking program. You may wish to consider the suggestions made in bold print. We realise that you may well have good reason not to take this further If you do decide to refer your patient for investigation you may find it useful to send this printout to the clinic of your choice. This project has been funded by GGHB and has the approval of the GP's Subcommittee of AMC.

When there are no complicating factors, simple common sense measures are proposed. Benefit is unlikely to be achieved immediately, and so the patient will have to be suitably motivated to gain from the self-help measures suggested. The specialist sisters are ideally suited to this task. In addition, they can give advice on bladder retraining, fluid intake and diet. They are also able to teach pelvic floor exercises when indicated.

The centre has a variety of educational material available to help the incontinent and their carers. This is in the form of video displays, visual aids and leaflets. Many of the leaflets have been produced by the centre. There is also a static display of incontinence aids and appliances for demonstration purposes. These aids feature in the Greater Glasgow Health Board "Best Buy" guide which the staff at the centre helped to produce.

Assistance and education to carers

The centre is playing an increasing role locally in the education of carers. These activities extend beyond the centre, with the staff going out to give talks to interested parties. Table 2 shows that since the centre opened 3290 professionals have attended teaching sessions given by the staff. In partnership with Age Concern Scotland a series of courses has been initiated for carers in residential homes and in the community at large. Some of the activities are self-financing and income generation is being developed to permit expansion of the service.

Table 2 Usage of Continence Resource Centre August 1989–February 1992

Telephone advice	*Patient attendances*	*Professional attendances*	*Teaching and requests for information and instruction*
7025	1045	3290	1446

Audit of the nature and level of demand for the Resource Centre

Shortly after opening, the Resource Centre was publicised by circulating leaflets to potentially interested groups throughout the Greater Glasgow Health Board area. These included leisure and sport centres, libraries, retail pharmacists, health centres and community centres. In addition, it has regularly been featured in newspaper articles locally and has been highlighted in a BBC Scotland news programme. A postal survey of the first 100 patients who attended the centre was carried out (Table 3); 97% of the respondents found the centre helpful and 39% recommended the centre to others; 66% followed up the advice to obtain further professional help. A more sophisticated audit is under way under the auspices of the University Department of Public Health.

Research

From the outset the staff at the centre have been actively involved in research. In association with Greater Glasgow Health Board's Incontinence Resource Assessment Group and the Common Services Agency Commodity Panel, the centre has produced protocols and been involved in trials of incontinence aids. This information has been used to help in the preparation of a Glasgow "Best Buy" guide. The "Best Buy" aid may not necessarily be the cheapest but is the most efficient all round performer.

A database has been set up of all patients who have attended the centre and this will be used to assess the potential needs of the Greater Glasgow Area Health Board population. In the past this information has not been readily available to the planners of health care needs. Confidentiality codes are observed.

Table 3 Results of Postal Survey

No of letters sent	100
No of replies	75
Of those who responded (%)	
"Cure"	16
Improvement	76
No improvement	8
Found centre helpful	97
No value	0
Recommended centre to others	39
Found further help with	
GP	29
District nurse	13
Hospital specialist	24

Note It is recognised that the survey is simplistic but it constituted an important part of the stated case for permanent funding. More sophisticated and objective audit has been established under the auspices of Glasgow University Department of Public Health.

Discussion

Table 2 demonstrates the need for a Continence Resource Centre. The telephone advisory service is a major success, with 1746 patients having used it in the first 31 months of operation. This is an ideal method of encouraging otherwise silent sufferers to come forward for help. It has also been of great help to those who are housebound or find it difficult to attend. Extensive advice can be given over the telephone.

The educational aspect of the centre's work has had a great impact on the local awareness of and interest in incontinence. Teaching larger groups of carers correct techniques of continence management benefits more sufferers than if the centre were to confine its activities to an individual patient basis. The specialist sisters have provided teaching sessions to home helps, general practitioners, nursing staff of all grades, health visitors and voluntary organisations. Although designated the Resource Centre for the Greater Glasgow Area Health Board, staff respond to requests for advice and tuition from other sources (Dawes *et al.*, 1991).

The activities and use made of the Continence Resource Centre exceed all expectations and it is perceived to be cost-effective. Expertise in assessing products for the "Best Buy" guide has helped to rationalise the use of available funds, a valuable aid in resource management. Educating sufferers and carers in correct techniques is cost-effective and makes more efficient use of available resources.

The centre, originally funded as a pilot project, has now achieved permanent status to serve Greater Glasgow Health Board, clear recognition that the current annual outlay of £44,000 is a small price to pay for improved management and cost efficiency. The potential for income generation was subsequently realised and is being developed. The Resource Centre established many of the functions recommended in the Department of Health Agenda for Action on Continence (Saunderson, 1991) and is being considered as a prototype for a service for Scotland.

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Preliminary Results of Concurrent Cisplatin and Radiation Therapy in Locally Advanced Bladder Cancer

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Summary—Between March 1981 and March 1990, 15 patients with locally advanced transitional cell carcinoma of the bladder were treated concurrently with cisplatin and radiotherapy. Treatment comprised a radiation dose of 40–50 Gy in 20–25 fractions over 4–5 weeks and intravenous infusion of cisplatin with hydration during days 1–5 and 22–26. The total scheduled dose of cisplatin was 200 mg. A complete response (CR) was seen in 3 patients (2 T2 tumours and 1 T3) and the other 12 were regarded as partial responders. Two of the 12 partial responders (1 T2 tumour and 1 T4) underwent cystectomy after treatment, but 9 patients (2 T2, 6 T3 and 1 T4) underwent only transurethral resection. The remaining patient (with a T4 tumour) died from systemic disease, further treatment not being possible because of unrelated heart failure. In 3 CR patients and 9 with a partial response (PR), bladder function was preserved and they have survived for a mean of 18.3 months (range 5–47) after therapy. Although 4 patients in this group had recurrent bladder tumours and 1 died from cancer in another part of the body, 7 have survived with normal bladder function and no recurrence.

It is concluded that concurrent cisplatin and radiation therapy is a safe and viable regimen and may be considered as a means of preserving the bladder in patients with locally advanced transitional cell carcinoma.

In the treatment of advanced bladder cancer, preoperative radiotherapy and subsequent total cystectomy have been reported to be relatively effective with regard to local tumour control and survival (Herr, 1985). In recent years, however, trials using cisplatin combined with radiotherapy have been performed and shown to have a beneficial effect on advanced transitional cell carcinoma (Soloway *et al.*, 1982; Jakse *et al.*, 1985; Shipley *et al.*, 1987; Sauer *et al.*, 1988). We have also reported preliminary results following the concurrent use of cisplatin and radiation therapy in 13 patients with advanced transitional cell carcinoma; 3 complete responses were achieved in 4 patients with large, metastatic, evaluable masses (Yoshioka *et al.*, 1987). Because of this high complete response rate, we decided to combine cisplatin and radiotheraphy as initial treatment for locally advanced transitional cell carcinoma. The results showed that cystectomy could be avoided even in patients who would otherwise have undergone radical total cystectomy.

In this report we have evaluated concurrent cisplatin and radiation therapy and discuss its potential as a means of preserving the bladder in patients with locally advanced bladder cancer.

Patients and Methods

Between March 1981 and March 1990, 32 patients with advanced transitional cell carcinoma were treated with concurrent cisplatin and radiation therapy. Seven patients had a local recurrence or lymph node metastasis after radical surgery and 15 had locally advanced bladder cancer. In 8 patients the treatment was given as post-operative adjuvant

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therapy and in 2 cases as palliative treatment for bone metastasis.

This study has focused on the 15 patients with advanced bladder cancer (14 males, 1 female) and their details are summarised in Table 1. Their average age was 65 years (range 54–79). All were evaluated according to their clinical history and the results of intravenous urography, CT scan, urine cytology, cystoscopy and transurethral biopsy. All patients had advanced bladder cancer (5 T2 tumours, 7 T3 and 3 T4) and were recorded as class 5 for urine cytology with Papanicolaou staining.

The schedule of cisplatin and radiation therapy is shown in Figure 1. Cisplatin was administered a few hours after radiotherapy, the dosage being 20 mg cisplatin with 500 ml saline given over 5 h, followed by sufficient hydration to reduce nephrotoxicity. Hydrocortisone was used concurrently with cisplatin to reduce the incidence of side effects. An anti-emetic agent was given to patients with severe gastrointestinal symptoms. One course of cisplatin lasted for 5 consecutive days and patients received a second course during the fourth week whenever possible. Ten patients completed a full course of cisplatin treatment but the other 5 received a smaller dose depending on renal function (60–180 mg). The mean dosage was 172.7 mg.

With ^{60}Co as the radiation source, small pelvic field radiation therapy was delivered to the anterior and posterior portals. Treatment consisted of 40 Gy/20 fractions/4 weeks or 50 Gy/25 fractions/5 weeks to the tumour. The mean dosage was 47.2 Gy (range 40–58).

Table 1 Details of 15 Patients

Mean age (range) (years)	65.0 (54–79)
Male	14
Female	1
Grade 2	9
Grade 3	6
Clinical category	
T2	5
T3	7
T4	3
Hydronephrosis	3

Clinical response was evaluated every 2 weeks, mainly on the basis of intravenous urography, CT scan, urine cytology and cystoscopy (including biopsy). A complete response was defined as complete disappearance of the tumour from imaging studies, together with negative cytology and negative biopsy. A partial response was defined as >50% decrease in evaluable masses; in other cases progressive disease (PD) was judged to have occurred. Approximately 2 weeks after completing treatment the partial responders underwent deep muscle transurethral resection and it was then decided whether or not to perform radical cystectomy.

Follow-up was performed every 2 weeks with repeat urine cytology, and every 3 months with imaging studies, including CT scan. Transurethral biopsy was done every 6 months.

Results

Of 15 patients with bladder tumours a complete response was achieved in 3 and a partial response in 12. Two of the partial responders underwent total cystectomy, 12 patients avoided cystectomy, and 1 patient (case 2) did not undergo surgery owing to congestive heart disease which had been diagnosed before treatment (Table 2). This patient maintained a partial response for 6 months and died of lung metastasis 17 months after treatment.

Microscopic examination of the bladder tumours of the 2 patients who underwent total cystectomy revealed that the lesions which had invaded the bladder wall were markedly constrained. Case 1 was admitted in a pre-uraemic state caused by advanced bladder cancer and lymph node metastases were seen at lymphangiography. Total cystectomy was therefore performed after chemotherapy and radiotherapy, but pathological specimens showed that the organic structure of the carcinoma had been largely destroyed, while nuclear pyknosis and karyorrhexis were found in large areas of the

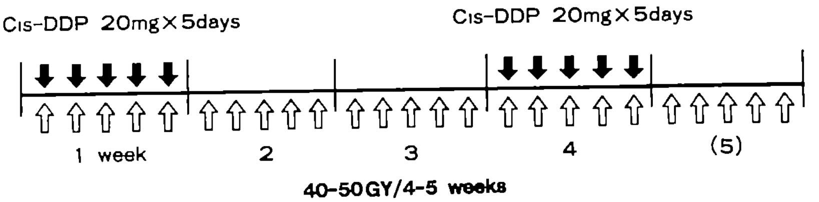

Fig. 1 Schedule of concurrent cisplatin and radiation therapy

Table 2 Results of Treatment

Case no.	*Age (years)*	*Sex*	*Clinical category, grade*	*RT (Gy)*	*Cisplatin (mg)*	*Clinical response*	*Surgical procedure*	*Pathology*	*Recurrence*	*Follow-up (months)*
1	54	M	T4, G3	50 1	70	PR	Cystectomy	pT3a, G3		52, Alive
2	68	M	T4, G3	50	160	PR	Not done		+	17, Dead
3	56	M	T3, G2	40	200	PR	TUR	pT2, G2		47, Alive
4	75	M	T2, G2	58	200	PR	TUR	p0		21, Dead*
5	54	M	T2+is, G2	50	200	PR	Cystectomy	p0		35, Alive
6	73	M	T2, G2	40	60	CR	Not done			24, Alive
7	59	M	T3, G3	50	200	PR	TUR	pT2, G3		28, Alive
8	75	M	T3, G2	50	180	CR	Not done		+	19, Alive
9	72	M	T3, G3	40	200	PR	TUR	pT1, G3		17, Alive
10	62	M	T3, G2	40	200	PR	TUR	pT2, G2	+	16, Alive
11	60	M	T3, G2	50	200	PR	TUR	pT1, G2		13, Alive
12	64	M	T3, G2	50	220	PR	TUR	pT2, G2	+	13, Alive
13	61	F	T4, G3	50	200	PR	TUR	pT2, G3	+	8, Alive
14	63	M	T2+is, G3	40	100	PR	TUR	pTis, G3		8, Alive
15	79	M	T2, G2	50	200	CR	Not done			5, Alive

*Due to a second primary tumour.

tumours. Degenerated cancer cells were also dispersed throughout the necrotic tissue and the small pelvic lymph node metastases diagnosed before treatment had been completely eliminated. In case 5, bladder capacity at presentation was approximately 150 ml because of carcinoma *in situ* with invasion. After treatment the patient's bladder contracted, causing bilateral hydronephrosis.

Total cystectomy had to be performed, but examination showed that the tumour cells had completely disappeared. These 2 patients have survived without recurrence for more than 2 years.

In the 12 patients whose bladder could be preserved, 3 achieved a complete response and 9 a partial response. Deep-muscle transurethral resections (TUR) were carried out in partial responders and marked contraction of the tumours and downstaging were observed in all TUR specimens (Fig. 2). In case 6, histological examination showed that the tumour had completely disappeared. Bladder irritability often followed TUR but subsided within 1 month. None of these patients had a contracted bladder. One patient died from rhabdomyosarcoma of the lower extremity but the remaining patients are still alive: the mean follow-up period was 18.3 months (range 5–47). Four patients had local superficial recurrence but this was well controlled with TUR. As a result, 7 patients with advanced bladder cancer were treated successfully and retained normal bladder function: the mean follow-up period was 20.3 months (range 5–47) (Table 3).

The following side effects were observed: loss of appetite in 12 patients, nausea in 5, leukopenia (<3000/mm^3) in 5, thrombocytopenia (<10^5/mm^3) in 2, diarrhoea in 6 and radiation-induced erythema in 2. All of these side effects were well tolerated and in no case did they cause therapy to be discontinued.

Discussion

Treatment of advanced, high grade transitional cell carcinoma is one of the most difficult therapeutic challenges for the urologist. Cisplatin monotherapy achieved CR in 8 to 14% of patients (Herr, 1980). Multichemotherapy, in which cisplatin was used as the primary agent, resulted in CR in 7 to 37% of treated patients (Schwartz *et al.*, 1983; Sternberg *et al.*, 1988). These results, even with the M-VAC regimen (methotrexate, vinblastine, doxorubicin, cisplatin), are not satisfactory. In addition, a major problem for patients treated with combined chemotherapy is severe side effects, often necessitating withdrawal of treatment. Radical irradiation, on

Table 3 Results following Surgery

	Alive				*Dead*	
	With bladder		*With cystectomy*		*With bladder*	
Clinical response	*NED*	*WED*	*NED*	*WED*	*NED*	*WED*
CR (3)	2	1	0	0	0	0
PR (12)	5	3	2	0	1	1
Total (15)	7	4	2	0	1	1

NED = no evidence of disease
WED = with evidence of disease

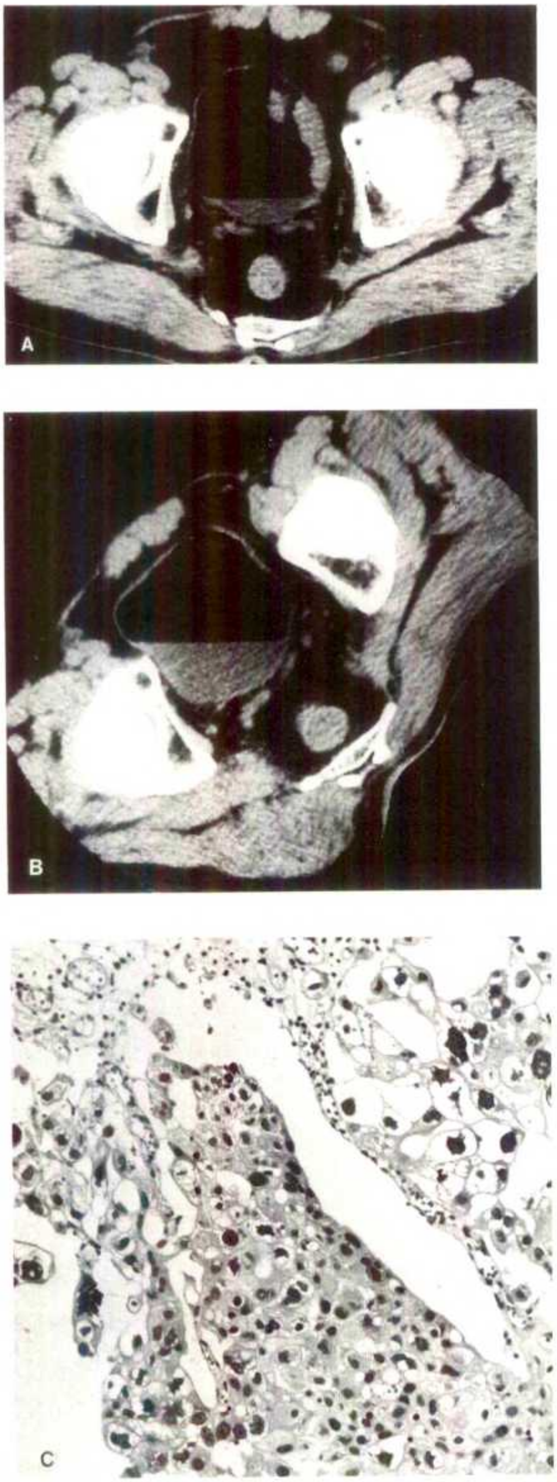

Fig. 2 Case 7. (A) Flat bladder tumours ascending the left bladder wall. (B) Almost normal findings on CT scan after treatment. (C) Cytoplasmic vacuolation, nuclear pyknosis and karyorrhexis are seen in most of the tumour. (H and E × 75).

the other hand, has been reported to achieve CR in approximately 40 to 43.9% of patients (Bloom *et al.*, 1982; Smaaland *et al.*, 1991). Smaaland *et al.* (1991) reported a significant advantage with >50 Gy, obtaining a complete response in 58.2% of patients, whereas <55 Gy produced CR in only 28.8%. However, the irradiation dose is inherently limited because of damage to normal tissue and so the CR rate is also limited.

In 1982, Soloway *et al.* reported a CR rate as high as 67.5% when using cisplatin combined with radiation therapy. Some other studies have also achieved a CR rate of about 77% in muscle-invading bladder cancer (Jakse *et al.*, 1985; Shipley *et al.*, 1987) and Jakse *et al.* (1987) also reported a CR rate of 82% using a modified regime with doxorubicin. In 1988, Sauer *et al.* described a treatment approach identical to ours and achieved a very high complete response rate (77%) and bladder preservation rate (83%). These results are obviously better than those of other systemic chemotherapies or radical irradiation alone. In our previous report (Yoshioka *et al.*, 1987), the patients with local recurrence or bulky lymph node metastasis after radical cystectomy were treated with cisplatin plus radiation therapy. Of these 4 patients with evaluable masses, 3 achieved a complete response and 1 had progressive disease. Two patients rated as CR died from metastasis to the liver. The other complete responder has survived without recurrence 48 months after treatment. We subsequently employed the treatment as initial therapy. In this series the CR rate (20%) was not so high, but it was particularly satisfactory that in 12 patients for whom cystectomy had been initially indicated, bladder function was preserved (mean follow-up 18.3 months). Although 4 of 12 patients suffered recurrent bladder tumours, it should be noted that these lesions were low grade and initial stage. It is encouraging that 7 patients have survived with normal bladder function without recurrence (mean follow-up 20.3 months).

These results suggest that concurrent cisplatin and radiation therapy is an effective initial treatment in patients with advanced transitional cell carcinoma, without the need for major surgery. Prout *et al.* (1990) reported a 43% bladder maintenance rate (without recurrence) in 53 invasive bladder cancer patients treated with multidrug chemotherapy plus cisplatin and radiotherapy, and reported a significantly higher rate (86 and 81%) among the complete responders. It is debatable whether patients with a positive TUR result after treatment can preserve their bladder function, but our results suggest that, given extensive debulking TUR after chemotherapy and radiotherapy, these patients can also be expected to maintain normal bladder function without tumour. In fact, all TUR specimens showed marked degeneration and downstaging of the tumours. This treatment may also eradicate local subclinical metastases of perivesical tissue and pelvic lymph nodes and prevent the dispersion of cancer cells as a result of surgical procedures. In case 1, with lymph node metastases, lymph node dissection revealed no tumour involvement.

The optimum dose levels of cisplatin and radiation have not yet been established. Since the complications of radiotherapy (*e.g.* bladder contraction) will make bladder preservation less valuable, the radiation dose should be as low as possible. Jakse *et al.* (1985) reported contracted bladders in 3 of 22 patients with 60 Gy radiation plus cisplatin therapy. We have therefore used 40–50 Gy irradiation in combination with cisplatin, followed by transurethral resection, to preserve bladder function. At these dosage levels, late complications of the bladder were not observed and major surgery should be reserved for persistent or recurrent cancer. The scheduled dose of cisplatin was 200 mg/patient but a favourable response was obtained with a smaller dosage in cases 1 and 6. This suggests that cisplatin can possibly be decreased to a minimum with maximum therapeutic effect when used concurrently with radiation. The synergistic effect achieved through the combination of cisplatin and irradiation has not yet been elucidated. However, previous studies have shown that cisplatin may inhibit repair of DNA damage induced by irradiation and act as a radiation sensitiser (Jakse *et al.*, 1985, 1987; Shipley *et al.*, 1987). Further study is required in a larger series to establish the optimum dose level.

It is concluded that concurrent cisplatin and radiation therapy is effective as initial treatment for transitional cell carcinoma, especially for deeply invasive bladder cancer, and may obviate total cystectomy in carefully selected patients. In order to improve the quality of life of patients with locally invasive urinary tract cancer, further investigation of this combined therapy should be of value.

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Cold Sensation and Bladder Instability in Patients with Outflow Obstruction due to Benign Prostatic Hyperplasia

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Summary—A series of 73 patients with bladder outflow obstruction caused by benign prostatic hyperplasia underwent urodynamic investigation, including the cold water test. The presence of detrusor instability was associated with a higher urethral opening pressure, maximum detrusor pressure and detrusor pressure at maximum flow. Instability was more common and more pronounced in patients with a lack of cold sensation, but there were some patients who, whilst lacking cold sensation, still possessed the cold reflex. This suggests partial denervation of the bladder or some form of altered modulation of sensory activity within the spinal cord or central nervous system. On the other hand, some of the patients lacked cold sensation but showed a stable detrusor and a high maximum cystometric capacity. This leads to the conclusion that there are different mechanisms by which the bladder reacts to outflow obstruction.

Infravesical obstruction is a condition which often interferes dramatically with bladder function and plays an important role in the nature of the patient's symptoms. Detrusor instability in particular has emerged as a major cause of frequency and urgency of micturition in obstructed patients, with the incidence of instability in obstructed patients ranging from 45 to 80% (Abrams and Feneley, 1978; Speakman *et al.*, 1987).

The most common form of outflow obstruction is benign prostatic hyperplasia (BPH). Schaefer (1983) showed that bladder outlet obstruction (BOO) resulting from BPH was mainly of a compressive type, *i.e.* characterised by an increase in urethral opening pressure. The reason is external compression of the flow controlling zone in the proximal urethra owing to enlarged prostatic lobes.

Specific cold receptors have been found in the feline bladder mucosa (Fall *et al.*, 1987). They also seem to be present in man and cold sensation is most often absent in patients with neurogenic lesions (Tammela *et al.*, 1989).

The aim of the present work was to investigate the correlation between cold sensation and detrusor instability and their association with the compressive component of BOO caused by BPH with regard to the pathophysiology of instability.

Patients and Methods

The series comprised 73 consecutive patients aged 48 to 80 years (mean 64) with BOO due to BPH; they were taken from the routine waiting list for prostatic surgery. All were assessed by means of symptom analysis, rectal examination, urological ultrasound including investigation of the kidneys, bladder and prostate, and physiological free-flow uroflowmetry. All patients showed both a clinical and a urodynamic pattern of BOO, which was defined in terms of pressure flow study either as a maximum flow rate <12 ml/s with a maximum detrusor pressure >45 cm water, or as a maximum flow rate >15 ml/s with a maximum detrusor pressure >75 cm water. Patients with a suspicion of prostatic carcinoma and a history of previous urinary tract surgery, acute retention of urine or neurological disease were excluded.

The patients underwent medium-fill water cystometry (50 ml/min) using 0.9% saline at room

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temperature and the presence of unstable contractions (> 15 cm water) was sought in response to filling, coughing and changing of posture. The bladder was filled through a 12 F Nelaton transurethral catheter and the intravesical pressure was recorded using another 4 F transurethral catheter. Intra-abdominal (p_{abd}) pressure was measured through a 4 F rectal balloon catheter. Detrusor pressure (p_{det}) was derived electronically by substracting p_{abd} from the intravesical pressure. After cystometry, the catheter used for filling was removed and a simultaneous pressure-flow electromyographic study performed. The cooling test was then performed in a supine position by infusing 100 ml of saline at 0°C into the empty bladder through a transurethral 8–12 F catheter in 10 to 20 s and monitoring the intravesical pressure through another 4 F transurethral catheter for 5 to 8 min. After injection of the iced water the patient was asked whether he could feel anything in his bladder and was then asked to describe the sensation. The methods, definitions and units conformed to the standards proposed by the International Continence Society (Abrams *et al.*, 1988).

The patients were evaluated in terms of first sensation (FS) in cystometry, maximum cystometric capacity (MCC), urethral opening pressure ($p_{det,\ open}$), maximum detrusor pressure ($p_{det,\ max}$), detrusor pressure at maximum flow ($p_{det,\ Qmax}$), instability during cystometry and during the cold water test (contraction ≥ 15 cm water), including the amplitude of maximum contraction, and the ability to feel the cold water in the urinary bladder.

The chi-squared test and Kruskal-Wallis test were used for statistical analysis. Differences were regarded as significant at $P < 0.05$.

Results

The 73 patients were divided into 2 groups, firstly according to detrusor stability (n = 44) or instability (n = 29) in cystometry (Table 1), and secondly according to their ability to feel the cold water (n = 44) or not (n = 29) (Table 2). They were then divided into 4 groups: cold sensation positive/stable bladder (n = 33), cold sensation positive/unstable bladder (n = 11), cold sensation lacking/stable bladder (n = 11) and cold sensation lacking/unstable bladder (n = 18) (Table 3).

Table 1 Urodynamic Parameters in Patients according to Detrusor Stability or Instability in Cystometry

Parameter	*Instability (n=44) Mean (SD)*	*Stability (n=29) Mean (SD)*	*P (Kruskal-Wallis test)*
FS (ml)	150 (56)	195 (101)	0.0615
MCC (ml)	329 (93)	473 (153)	0.0001
$p_{det\ open}$ (cm H_2O)	129 (63)	89 (50)	0.0076
$p_{det\ max}$ (cm H_2O)	145 (73)	98 (52)	0.0090
$p_{det\ Qmax}$ (cm H_2O)	121 (60)	87 (49)	0.0192
Age (years)	64 (6)	63 (6)	0.2605

The groups did not differ significantly in their mean ages. $p_{det\ open}$, $p_{dt\ max}$ and $p_{det\ Qmax}$ were significantly higher in the unstable bladders than in the stable ones, whereas MCC was significantly lower (Table 1). On the other hand, no significant differences in these parameters were found between those able to feel the cold water and those unable to do so (Table 2).

Detrusor instability was significantly more common in the patients with a lack of cold sensation, 18 of 29 (62%), than in those with normal sensation, 11 of 44 (25%) ($P = 0.002$). The maximum unstable contractions in cystometry were also more pronounced in the instability patients with a lack of cold sensation (44 ± 18 cmH_2O) than in those with this sensation (21 ± 4 cmH_2O) ($P = 0.0007$). The ice-water test induced contractions > 15 cm water in 17 patients (23%), 3 of whom did not show instability during cystometry. Nine of these 17 patients lacked cold sensation (53%), while 19 of 56 patients not showing such contractions during the ice-water test did so (34%).

FS and MCC were highest and micturition detrusor pressures lowest in the patients with a lack of cold sensation but a stable detrusor (Table 3).

Discussion

A higher compressive component was found to be present in the patients with prostatic obstruction showing detrusor instability than in the stable patients, and instability was more common and more pronounced in the patients with a lack of cold sensation than in those with normal sensation.

It has been speculated that the severity and occurrence of bladder instability may be linked to the degree of outflow obstruction, but this is a matter for debate. No correlation has been found in man between the severity of detrusor instability and the degree of outflow obstruction (Andersen, 1982; Coolsaet *et al.*, 1984), although a correlation has been reported between the latter and the

Table 2 Urodynamic Parameters in Patients according to the Ability to feel Cold Water in the Bladder

Parameter	*Cold sensation present (n=44) Mean (SD)*	*Cold sensation absent (n=29) Mean (SD)*	*P (Kruskal-Wallis test)*
FS (ml)	169 (57)	192 (106)	NS
MCC (ml)	420 (144)	414 (162)	NS
$p_{\mathrm{det\ open}}$ (cm H_2O)	103 (55)	107 (56)	NS
$p_{\mathrm{det\ max}}$ (cm H_2O)	116 (61)	117 (66)	NS
$p_{\mathrm{det\ Qmax}}$ (cm H_2O)	99 (50)	103 (59)	NS
Age (years)	63 (7)	63 (6)	NS

Table 3 Urodynamic Parameters in Patients according to the Ability to feel Cold Water and Detrusor Stability or Instability in Cystometry

Parameter	*Cold sensation present, stable (n=33) mean (SD)*	*Cold sensation absent, stable (n=11) mean (SD)*	*Cold sensation present, unstable (n=18) Mean (SD)*	*Cold sensation absent, unstable (n=18) Mean (SD)*
FS (ml)	176 (83)	252 (132)	145 (41)	153 (64)
MCC (ml)	451 (139)	539 (181)	321 (114)	333 (80)
$p_{\mathrm{det\ open}}$ (cm H_2O)	92 (46)	81 (47)	135 (60)	124 (61)
$p_{\mathrm{det\ max}}$ (cm H_2O)	103 (56)	82 (49)	152 (75)	140 (73)
$p_{\mathrm{det\ Qmax}}$ (cm H_2O)	90 (51)	80 (50)	127 (51)	118 (62)
Age (years)	63 (7)	61 (5)	64 (6)	65 (6)

occurrence of bladder instability (Cucchi, 1990). The presence of instability in our patients was found to be associated with a higher urethral opening pressure, which characterises the compressive component of bladder outflow obstruction arising from benign prostatic hyperplasia (Schaefer, 1983; Cucchi, 1990).

The pathophysiology that leads to unstable bladder contractions is unclear, but changes in peripheral or central nervous control or alterations in the smooth muscle have been postulated. Several theories have been suggested, including changes in the density of normal relaxing beta-adrenoreceptors to contraction-mediating alpha-receptors (Perlberg and Caine, 1982), increased afferent impulse transmission to the bladder from the prostate and bladder neck (Yeates, 1972; Chalfin and Bradley, 1982) or a lowered threshold of the stretch reflex in the bladder wall (Yeates, 1972) and age-related reduction in cholinesterase-positive nerves associated with the detrusor muscle (Abrams, 1985; Gilpin *et al.*, 1986). The present series nevertheless did not reveal any differences in age between the groups showing detrusor stability and instability.

Obstructive detrusor instability has also been explained by denervation, resulting in a state of post-junctional supersensitivity (Sibley, 1987). In accordance with this, a reduction in the autonomic innervation has been demonstrated in obstructed bladders in man (Gosling *et al.*, 1986; Sibley, 1987). Selective denervation in obstructed bladders has also been suggested (Kato *et al.*, 1990), but it is not clear why the autonomic innervation of the detrusor muscle should become damaged in the presence of outflow obstruction. Possible mechanisms that have been suggested include the effects of the rise in intravesical pressure, relative ischaemia of the hypertrophied bladder wall and derangement of the system of trophic factors responsible for maintaining a normal pattern of innervation (Harrison *et al.*, 1987). It has recently been postulated, however, that obstructed bladder instability is mediated primarily by a myogenic mechanism rather than by nerves (Malmgren, 1989).

The existence of thermaesthesia of the bladder mucosa has been a source of controversy. Many earlier investigators denied it (Bors *et al.*, 1956), whereas others found it obvious (Gunterberg *et al.*, 1975). Fall *et al.* (1987) postulated on the basis of feline experiments that a pathway separate from the tension receptor system exists for the bladder cooling reflex, the receptors responsible having properties similar to those of cutaneous cold receptors (Lindström *et al.*, 1988). Our previous observations support the existence of cold receptors and a cooling reflex in man as well (Tammela *et al.*, 1989).

Cold sensation has most often been found to be absent in patients with neurogenic lesions (Tammela *et al.*, 1989) and no significant urodynamic differences could be found in the present series between the groups divided according to their ability to feel the cold water. Detrusor instability was more common in the patients with a lack of cold sensation, however, and unstable contractions were also more pronounced in such patients, which might support the theory of the development of smooth muscle hypersensitivity secondary to partial denervation of the obstructed bladder. Detrusor instability was also associated with a higher urethral opening pressure. On the other hand, the presence of a cold reflex with detrusor contractions in some of these patients argues against deafferentation and may indicate some form of altered modulation of sensory activity involving the spinal cord or central nervous system.

In conclusion, a correlation was observed between high urethral opening pressure and the occurrence of bladder instability; this was more common and more pronounced in patients with a lack of cold sensation, but some such patients did possess a cold reflex. This may suggest partial denervation or some form of altered modulation of sensory activity more centrally in patients with outflow obstruction. It would be interesting to test whether patients with a lack of cold sensation also lack other forms of bladder sensation. In fact, some patients with a lack of cold sensation in the present series did not show detrusor overactivity but had high FS and MCC. This, in common with the taking of bladder specimens, would offer scope for further investigation.

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Is Indoramin an Effective Alternative to Prostatectomy?

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Summary—Alpha-1-adrenergic antagonists are recommended for symptomatic treatment of patients awaiting prostatic surgery. Their efficacy has been confirmed in placebo controlled clinical trials, but to date no comparison of their effects with the results of subsequent prostatectomy has been made.

Fifty-five patients awaiting prostatectomy were assessed (by symptom scores and peak urinary flow rates) prior to treatment, on indoramin 20 mg *bd*, and 2 months following prostatectomy. Side effects while taking indoramin were experienced by 36% of patients. Despite an overall improvement in mean symptom scores, 26% of patients with obstructive and 30% of those with irritative symptoms who were assessed while taking indoramin failed to experience any improvement. Of the 31 patients assessed while on indoramin and again following surgery, prostatectomy produced a greater symptomatic relief than indoramin. The increase in peak flow rate following prostatectomy was 11.7 ml/s compared with 3.2 ml/s on indoramin. However, 5 patients preferred to continue taking indoramin rather than proceeding to surgery.

Indoramin is no substitute for prostatectomy. Although some patients might benefit from treatment while awaiting surgery, significant side effects may severely restrict its use for this purpose. The response to indoramin cannot be used as an accurate predictor of response to prostatectomy.

Indoramin is an alpha-1-adrenergic receptor antagonist which has been shown to be more effective than placebo in improving symptoms in patients with benign prostatic hyperplasia (Iacovou and Dunn, 1987; Chow *et al.*, 1990; Stott and Abrams, 1991). While controlled trials have demonstrated these apparent benefits, such studies usually involved selected patients and the tolerance and efficacy of indoramin in general urological practice are less clear. Having recently recruited patients for a large multi-centre trial of another alpha-1 receptor antagonist, we were aware that the majority of patients who might have been suitable for treatment were excluded from investigation because of the strict entry criteria imposed, and the results of that study might not be applicable to them. In addition, we know of no study directly comparing the efficacy of alpha receptor antagonists with prostatectomy.

The use of indoramin in an unselected group of patients awaiting prostatectomy, its value at predicting response and its effectiveness compared with the results of surgery have been monitored and the results are presented here.

Patients and Methods

A total of 55 patients who were on the waiting list for elective prostatectomy were treated with indoramin. Patients were excluded only if there were clear medical contraindications to alpha receptor antagonist therapy. Each patient was assessed by symptom score according to the method of Boyarsky *et al.* (1977), and by maximum urinary flow rates using a Urodyn 1000 (Dantec) uroflowmeter. Assessment was made prior to receiving indoramin 20 mg *bd*. The general practitioners were asked to prescribe the indoramin and to modify any existing antihypertensive therapy where appropriate in accordance with the data sheet recommendations

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for the use of indoramin. Assessment of symptom scores and urinary flow rates was repeated after 2 months' treatment on indoramin, usually just prior to prostatectomy. This assessment was repeated 2 months following surgery.

For the purpose of statistical analysis, patients with Boyarsky scores of 2 or less for obstructive or irritative scores were not regarded as having significant symptoms. Urinary flow rates with voided volumes greater than 100 ml were preferred, but flow rates where the voided volume was less than 100 ml on 3 successive occasions were included for analysis if the tracing was considered representative of the patient's normal voiding pattern.

All statistical analyses were performed using Student's paired t test, on the Minitab version 6 designed for the Apple Macintosh SE.

Results

Of the 55 patients who were prescribed indoramin, 20 experienced side effects (Table 1) and 7 stopped treatment as a result. Six more patients stopped because they failed to perceive any appreciable improvement in their symptoms and 1 patient was taken off medication following a myocardial infarction. There was an improvement in overall mean symptom scores which was statistically significant ($P<0.001$) and an increase in the overall mean peak urinary flow rates by 3.2 ml/s ($P<0.001$) in the 41 patients who could be assessed while on indoramin (Table 2). However, 10 of 38 patients (26%) with obstructive and 9 of 30 (30%) with irritative symptoms failed to improve on indoramin. Five patients preferred to continue taking indoramin because of the benefits experienced on this treatment.

Forty-three patients have undergone prostatectomy; surgery was postponed in 7 patients for medical or social reasons. One patient refused follow-up assessment, so that 42 patients have been assessed (Table 2). All patients with obstructive, and all but 1 with irritative symptoms, improved following surgery ($P<0.001$). The mean improvement in urinary flow rates was 11.5 ml/s ($P<0.001$). A temporary worsening of irritative symptoms and post-void dribbling was observed in several patients following prostatectomy, but in all cases this was short-lived.

Table 1 Side Effects

Symptom	*No. of patients*
Tiredness	11
Ataxia	3
Headache	3
Retrograde ejaculation	2
Nausea	2
Depression	1
Diarrhoea	1
Painful frontal sinuses	1
Abnormal liver function	1
Chlorine-like smell in urine	1

Table 2 Results of Treatment

	Before treatment (n=55)	*On indoramin (n=41)*	*After TURP (n=42)*
Obstructive symptoms (1–15)	7.3±3.5	4.2±3.6 ($P<0.001$)	1.1±1.4 ($P<0.001$)
Irritative symptoms (1–12)	4.1±2.3	2.8±1.9 ($P<0.001$)	2.1±1.9 ($P<0.001$)
Maximum urinary flow (ml/s)	10.1±3.7	13.3±5.8 ($P<0.001$)	21.6±9.8 ($P<0.001$)

A total of 31 patients were assessed both while on indoramin and subsequently after prostatectomy (Table 3). Surgery produced greater symptomatic improvement than indoramin. This was statistically significant for obstructive ($P<0.001$) but not for irritative symptoms. In these patients indoramin produced an increase in flow rate of 3.2 ml/s compared with 11.7 ml/s following surgery ($P<0.001$). Scatter plot diagrams of symptom scores and maximum urinary flow rates of patients assessed on indoramin and following prostatectomy can be seen in Figures 1 to 3. An improvement in all parameters in favour of prostatectomy can be observed.

Discussion

This experience has demonstrated that indoramin may benefit only 70 to 75% of patients suffering from symptoms secondary to bladder outflow obstruction. The incidence of side effects (36%) is similar to the 35% reported by Stott and Abrams (1991), but is higher than that reported in other series (Iacovou and Dunn, 1987; Chow *et al.*, 1990). The most frequently reported side effect was tiredness, which occurred in 11 patients. The report of ataxia suggests that postural hypotension may have occurred in at least 3 patients.

The exclusion of patients from trials because their urine flow parameters fall outside set limits has been disputed by Haylen *et al.* (1989) following

Table 3 Results in 31 Patients Assessed while on Indoramin and again following Prostatectomy

	Before treatment	*On indoramin*	*After TURP*	*TURP-indoramin*
Obstructive symptoms (1–15)	7.0±3.8	4.1±2.0 ($P<0.001$)	1.4±1.5 ($P<0.001$)	−2.7±2.9 ($P<0.001$)
Irritative symptoms (1–12)	4.1±2.0	2.8±1.8 ($P<0.001$)	2.1±1.9 ($P<0.001$)	−0.7±2.2 (NS)
Maximum urinary flow (ml/s)	10.3±3.9	13.5±6.4 ($P<0.002$)	22.0±9.8 ($P<0.001$)	8.5±10.4 ($P<0.001$)

construction of the Liverpool nomograms. For this reason we felt justified in including patients with voided volumes less than 100 ml. There was a statistically significant improvement in maximum urinary flow rates of 3.2 ml/s on indoramin. This improvement is in line with the previous reports of 4.9 ml/s (Chow *et al.*, 1990) and 1.7 ml/s (Stott and Abrams, 1991). However, compared with the improvement following prostatectomy of 11.7 ml/s, the clinical significance of the benefits of alpha receptor antagonists must be questioned.

Prostatectomy remains the gold standard treatment for bladder outflow obstruction. The value of indoramin, and possibly other similar agents, in the management of these patients may be limited by the high incidence of side effects. We tried to use the response to indoramin as a predictor of response to surgery. Unfortunately, there did not appear to be any correlation between the 2 methods of treatment. Failure to respond to indoramin could not be used a predictor of poor outcome following prostatectomy. Only 1 patient felt that indoramin offered a subjective improvement comparable with that of prostatectomy. Indoramin still has a role in our clinical practice for those patients who request medical management of their symptoms, and in those who are unfit for surgical treatment but are suitable for alpha-blocker therapy. We no longer prescribe indoramin for all patients on the waiting list even if their wait has been protracted.

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0.0       3.0       6.0       9.0      12.0      15.0
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Fig. 1 Obstructive symptoms in patients assessed both on indoramin and following prostatectomy. PreOb = before treatment. IndOb = on indoramin. TUROb = following prostatectomy

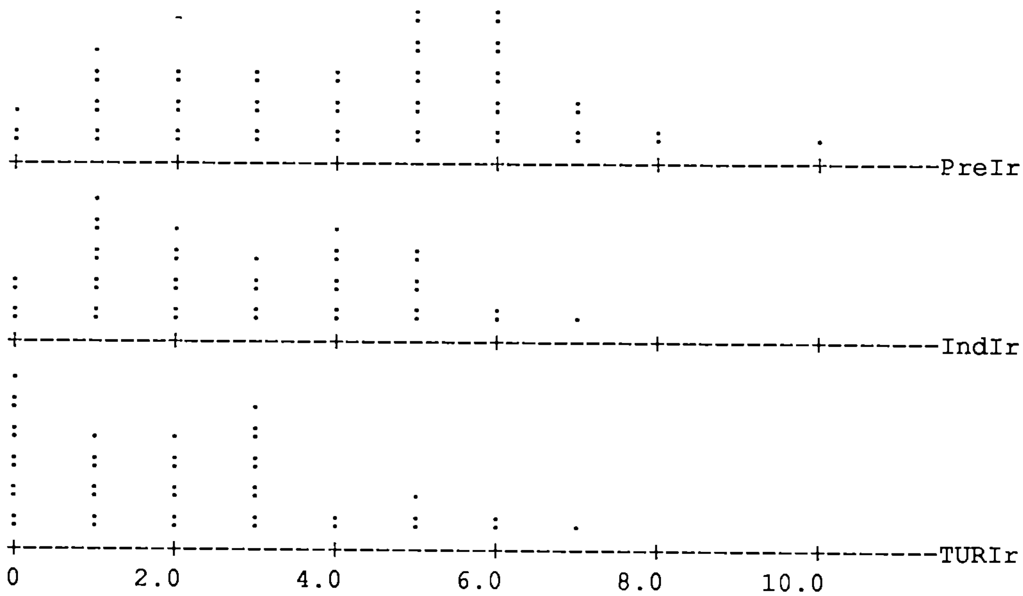

Fig. 2 Irritative symptoms in patients assessed both on indoramin and following prostatectomy PreIr = before treatment. IndIr = on indoramin. TURIr = following prostatectomy

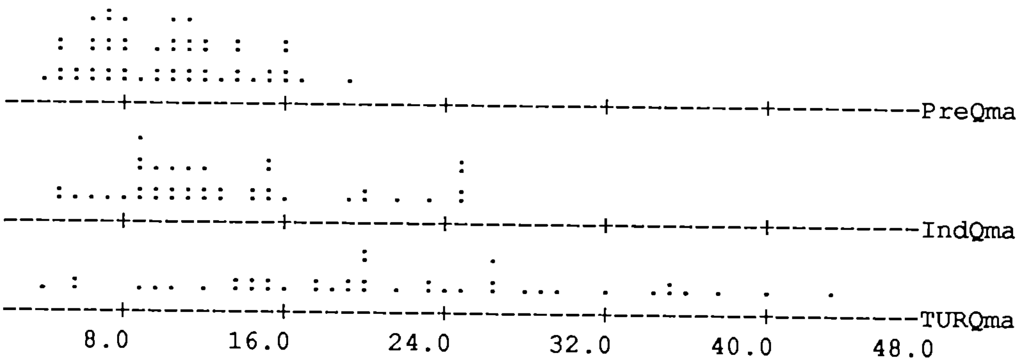

Fig. 3 Maximum urinary flow rates (ml/s) in patients assessed both on indoramin and following prostatectomy. PreQma = before treatment. IndQma = on indoramin. TURQma = following prostatectomy

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Outcome and Prognostic Factors in Patients with Advanced Prostate Cancer and Obstructive Uropathy

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Summary—In a series of 51 patients with prostate cancer and obstructive uropathy, unilateral or bilateral obstruction was identified in 22 (43%) and 29 (57%) respectively. This included a non-functioning kidney in 12 patients. In 86% of patients the T category was advanced. Bone metastases were present in 36 cases (71%); 19 patients (37%) had chronic retention. All patients with metastatic disease underwent hormonal manipulation and 43 underwent transurethral resection of the prostate. External beam radiotherapy, percutaneous nephrostomy and ureteric reimplantation were performed in 4, 5 and 1 patient respectively.

Actuarial survival of all 51 patients was 57 and 25% at 2 and 5 years. Presentation with bilateral or non-function did not predict a worse prognosis in comparison with patients with unilateral hydroureteronephrosis. Raised alkaline phosphatase and prostatic acid phosphatase were of no prognostic value, while creatinine reached marginal significance. A positive bone scan and raised urea were strongly predictive of a poor outlook. It was concluded that prostate cancer and obstructive uropathy should not uniformly imply a terminal event, and interventional therapy is justified with a 25% 5-year survival rate.

Obstructive uropathy is often regarded as the harbinger of poor prognosis in patients with pelvic malignancy. Relief of renal failure is discouraged, as it is recognised that the outlook for patients with colonic or bladder carcinoma and other malignant diseases is particularly poor (Brin *et al.*, 1975). A significant number of patients with prostate cancer present with advanced disease but, unlike those with other malignancies, they fare better because initially the tumour is sensitive to androgen withdrawal or suppression (Sandhu *et al.*, 1990). The importance of diagnosing obstructive uropathy lies in the potential reversibility of renal failure (Spital *et al.*, 1988) and improvement in survival (Ganem, 1957). The advent of endourology with percutaneous nephrostomy and ureteric stenting has significantly altered the management of obstructive uropathy in these patients (Singh *et al.*, 1979; Suryva and Provet, 1989). We report the effect of surgical management on 51 patients with obstructive uropathy and carcinoma of the prostate during a 10-year follow-up, and identify prognostic indices that may help to predict outcome.

Patients and Methods

In the period 1980 to 1990, 450 patients with histologically proven cancer of the prostate were seen at the University Hospital of South Manchester. Of these a subgroup (n = 51, 11%, mean age 73 years (range 57–87)) was identified as having obstructive uropathy. Intravenous urography (IVU), ultrasound (US) or computed tomography (CT) demonstrated unilateral and bilateral hydroureteronephrosis in 22 patients (43%) and 29 patients (57%) respectively. Twelve patients (23%) had a unilateral non-functioning kidney, making the management of the contralateral kidney critical. The following prognostic markers were investi-

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Based on a Poster Demonstration at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991 gated: presence of bone metastases, unilateral or bilateral hydroureteronephrosis, non-functioning kidney, serum creatinine, urea, prostatic acid phosphatase and alkaline phosphatase. All patients underwent intravenous urography and bone scanning with ^{99}Tc diphosphonate. Ultrasound, CT and diuretic renography with split level function were performed in 34 (66%), 35 (68%) and 13 (25%) patients respectively. In 44 patients (86%) the T category was advanced (T3/T4) and tumour grade was poorly differentiated in 25 men (50%). Bone metastases were present in 36 patients (71%). Clinically palpable nodes and CT examination revealed pelvic lymphadenopathy in 31 cases (60%). Painless retention was clinically evident in 19 patients (37%).

Treatment

All patients with bony metastatic disease (n = 36) were treated by hormonal manipulation (subcapsular orchiectomy or LHRH agonist). Apart from subcapsular orchiectomy, 43 patients (84%) required transurethral resection of the prostate (TURP); 16 (31%) required 2 TURPs and a further 9 (18%) needed 3 or more resections (maximum 4). Five patients required a nephrostomy, 1 underwent reimplantation of the ureter and another with synchronous bladder carcinoma underwent cystoprostatectomy and formation of an ileal conduit. Permanent suprapubic or urethral catheterisation due to detrusor sphincter involvement and incontinence was necessary in 4 patients. Radiotherapy was given to 4 patients with locally advanced disease (T2) and dilated upper tracts. All patients were followed thereafter in the prostate cancer clinic at 3 to 6 monthly intervals until death.

Statistical analysis

Data were analysed using the main frame BMDP statistical analysis package (BMDP statistical software INC). Actuarial survival curves were analysed using the Savage (Mantel-Cox) test.

Results

TURP (n = 43), insertion of nephrostomy (n = 5) and ureteric reimplantation (n = 1) lowered serum creatinine from a mean of 0.32 mmol/l to 0.16 mmol/l (normal range 0.01–0.12 mmol/l) within 1 month.

Actuarial survival of all 51 patients was 57 and 25% at 2 and 5 years respectively, with no difference in survival in the chronic retention group (n = 19) compared with the 32 patients who had a variety of symptoms such as haematuria, bone pain as well as acute retention (Fig. 1). Presentation with bilateral dilatation or non-function did not predict a worse prognosis in comparison with patients with unilateral hydroureteronephrosis (Fig. 2). Raised urea at diagnosis (n = 23; $P = 0.02$) and the presence of

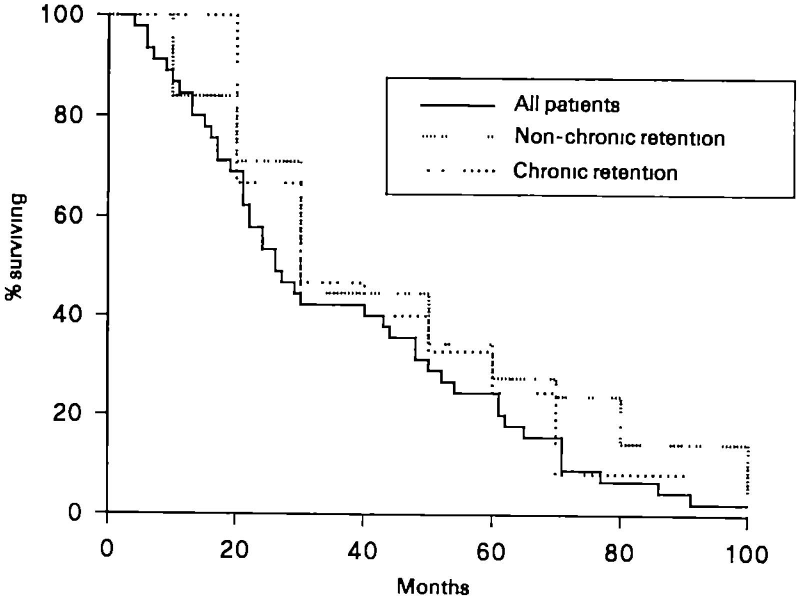

Fig. 1 Actuarial survival of all 51 patients and 19 patients with chronic retention compared with remaining 32 patients. No significant difference in survival.

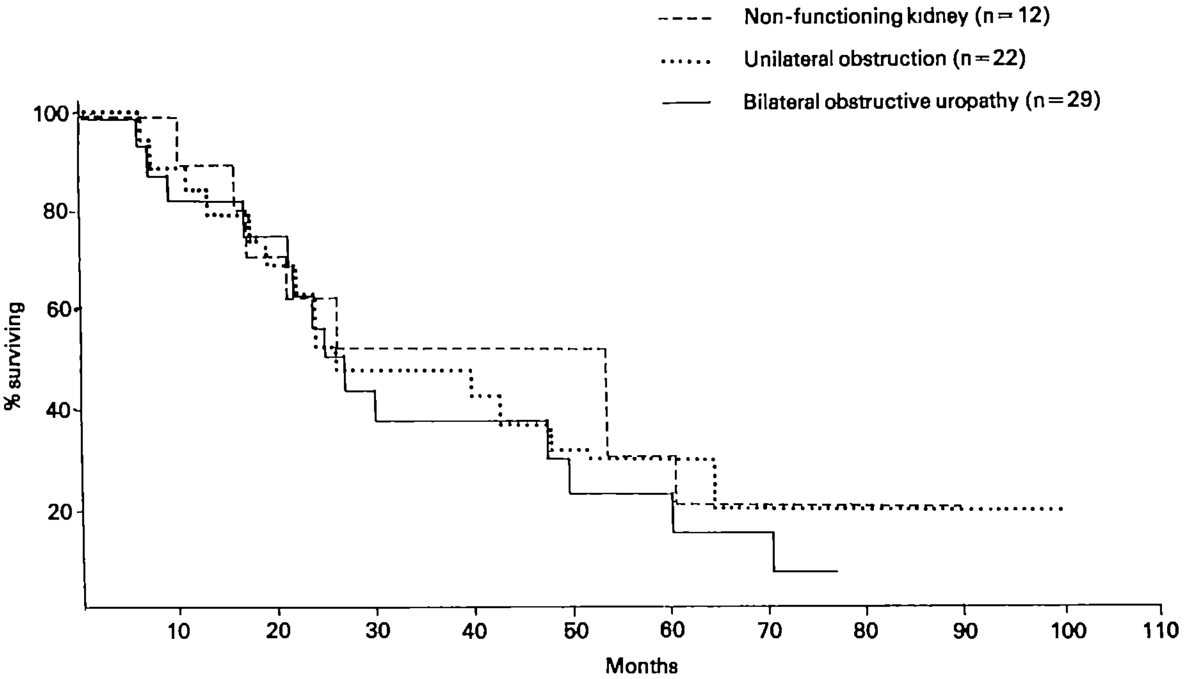

Fig. 2 Actuarial survival curves demonstrating no difference in survival with respect to non-function, unilateral or bilateral hydroureteronephrosis.

bone metastases (n = 36; $P = 0.002$) were strongly predictive of a poor outlook, with 5-year survival rates of 13% (Fig. 3) and 14% (Fig. 4) respectively compared with 47% and 58% in patients with a normal urea and negative bone scan at diagnosis. Elevated prostatic acid phosphatase and alkaline phosphatase did not predict a worse outlook (Fig. 3). Raised creatinine at diagnosis, however, (n = 28) was associated with a diminished 5-year survival rate of 16% compared with 40% in those patients (n = 23) with normal creatinine ($P = 0.06$) (Fig. 5).

Discussion

This study has examined the outcome of the clinical management of patients with advanced prostate cancer and obstructive uropathy. Invasive prostate cancer can cause deterioration in renal function from prostatic outflow obstruction (Sacks *et al.*, 1989) and ureteric obstruction by direct involvement, malignant retroperitoneal fibrosis (RPF), compression by lymph nodes and intramural metastases (Marks and Gallo, 1972; Khan and Utz, 1975). Bladder outlet obstruction is commonly reported (Varenhorst and Alund, 1985) and in the present series this occurred in 84% of cases. Hormonal manipulation on its own or with a channel TURP is the usual mode of therapy, as further prostate shrinkage after androgen deprivation is well recognised (Spirnak and Resnick, 1984; Varenhorst and Alund, 1985) irrespective of tumour volume and grade (Fleischmann and Catalona, 1985). Tumour progression with hormonal escape may necessitate further transurethral resections of prostate and in this study 16 patients (31%) required further resections (maximum 4). Sphincter involvement in advanced prostate cancer can produce distressing incontinence and 4 patients required suprapubic or urethral catheter urinary diversion.

Only 4 of 31 patients with pelvic lymphadenopathy were found to have extrinsic ureteric compression with malignant RPF; most ureteric obstruction was due to involvement of the vesicoureteric junction. TURP, internal stenting and ureteric reimplantation, especially in the presence of a large pelvic tumour mass (Kihl and Bratt, 1981), are appropriate in this situation. Presentation with bilateral hydroureteronephrosis or non-function did not predict a poor prognosis (Fig. 2) and therefore this finding should not uniformly imply a terminal event or hopeless prognosis. Aggressive treatment in selected cases can increase survival without an associated increase in morbidity (Khan and Utz,

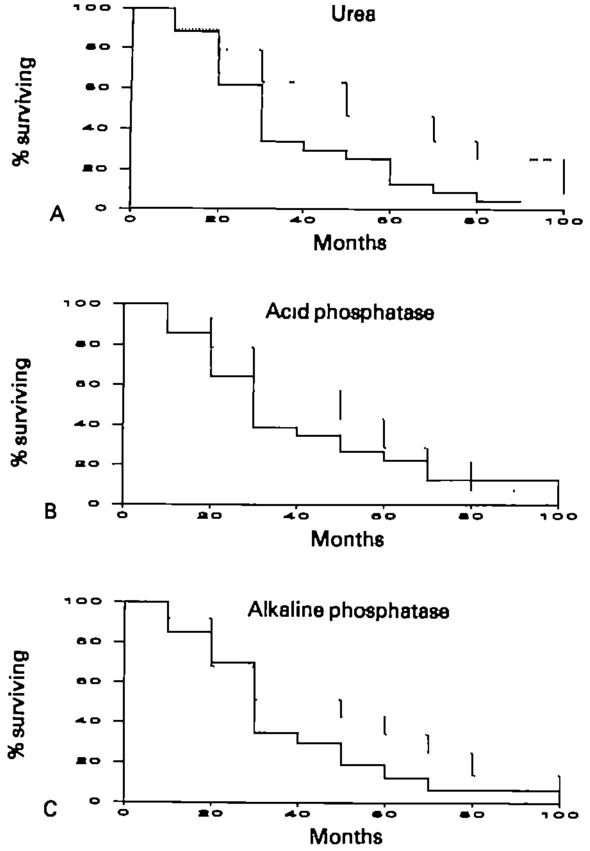

Fig. 3 Actuarial survival with respect to (A) Urea: significant difference ($P=0.02$) between raised urea at diagnosis (n = 23) (solid line) and normal urea (n = 28) (dotted line). (B) No significant difference between raised acid phosphatase at diagnosis (n = 31) (solid line) and normal acid phosphatase (n = 20) (dotted line). (C) No significant difference between raised alkaline phosphatase at diagnosis (n = 23) (solid line) and normal alkaline phosphatase (n = 28) (dotted line)

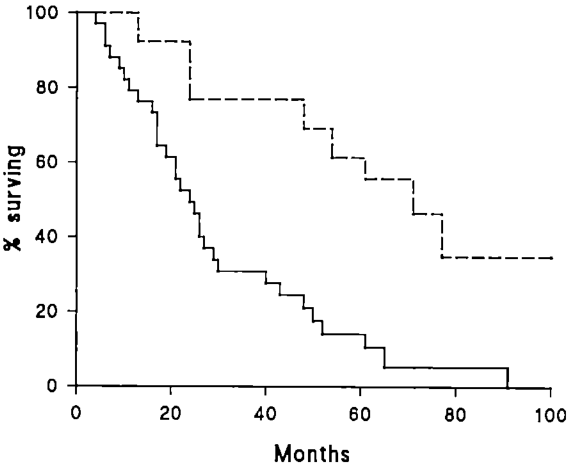

Fig. 4 Actuarial survival of 36 patients with positive bone scan (solid line) (14% 5-year survival) compared with 15 patients without bone metastases (dotted line) (58% 5-year survival) ($P=0.002$)

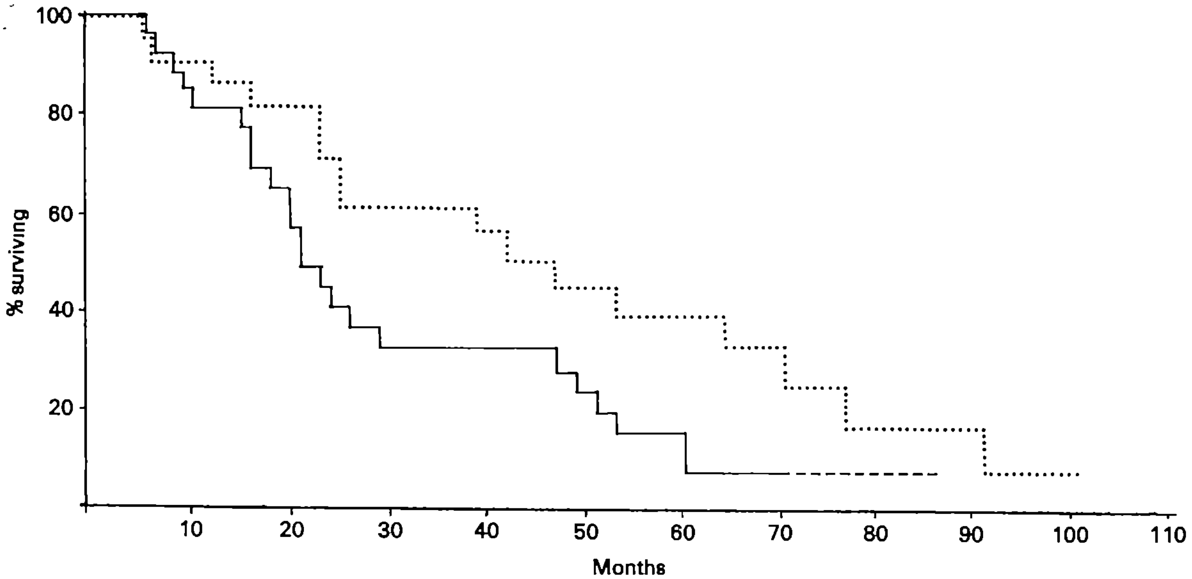

Fig. 5 Actuarial survival of 28 patients with raised creatinine at diagnosis (solid line) (16% 5-year survival) compared with 23 patients with normal creatinine (dotted line) (40% 5-year survival): marginal significance $P<0.06$

1975). Unilateral ureteric obstruction is clearly critical in patients with a single kidney and percutaneous nephrostomy (PCN) improves renal function, allowing time for additional adjunctive therapy to be used. In this series impaired renal function at diagnosis with a raised urea ($P=0.02$) and creatinine ($P<0.06$) was a poor prognostic sign, with 5-year survival rates of 13 and 16% compared with 47 and 40% in the remaining patients (Figs 3 and 5). This may in part reflect a greater incidence (57 *vs* 39%) of high grade tumour in the patients with renal impairment, although the incidence of bone metastases at diagnosis did not differ significantly (75 *vs* 65% respectively) between the 2 groups. In patients with unilateral obstruction PCN is not justified, but it can extend survival for patients with bilateral obstruction (Chang *et al.*, 1988). Progressive deterioration of the upper tracts following anti-androgenic treatment combined with surgical relief of bladder neck obstruction has a poor outlook independent of bone scan status (Ganem, 1957). With the advent of endourology the place of ileal loop diversion and cutaneous ureterostomy (Kihl and Bratt, 1981) for ureteric obstruction is limited. A decision to divert must be based on the disease status, availability of further therapy and the wishes of the patient and family (Richie and Ehrlich, 1979).

In summary, transurethral resection of the prostate has a low morbidity rate and patients may benefit from repeat resections, whilst upper tract dilatation and non-function do not predict a poor outlook. If retrograde ureteric stenting is difficult because of trigonal involvement it may be better in selected cases to replace the nephrostomy tube with an antegrade ureteric stent. Normally, unilateral obstruction does not require decompression as there is no advantage in survival. Patients with bone metastases and impaired renal function have a poor survival rate. Aggressive interventional therapy is justified, with 25% of patients alive at 5 years.

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Testicular Denervation. A New Surgical Procedure for Intractable Testicular Pain

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Summary—Chronic testicular pain has many different aetiologies. Identification and treatment of an underlying problem resolve the issue in most cases. However, a proportion of patients with chronic testicular pain have no demonstrable aetiological factor and pose a difficult treatment problem. All of these patients are initially treated by non-surgical measures. Various operations advocated in the literature for non-responders include epididymectomy, scrotal orchiectomy and inguinal orchiectomy, all of which have a significant failure rate. We describe a hitherto unreported operative procedure in a series of 4 patients, with immediate and lasting relief of their pain.

Chronic testicular pain is an interesting urological problem. Management is straightforward if an underlying condition is detectable on examination or investigation. Various causes in this context include infection, tumour, inguinal hernia, intermittent testicular torsion, hydrocele, spermatocele, varicocele, referred pain and trauma. However, in about 25% of patients with chronic testicular pain, no obvious pathology is found even when the most modern methods of evaluation and laboratory testing are carried out (Davis *et al.*, 1990). This condition has been variously named as orchiodynia, orchidalgia, orchialgia and testalgia. Patients with post-vasectomy testicular pain have also been grouped in this category if no local abnormality is demonstrable on clinical examination.

For the purposes of clinical discussion, a working definition of chronic orchialgia would be "intermittent or constant, unilateral or bilateral testicular pain, 3 months or longer in duration that significantly interferes with the daily activities of a patient so as to prompt him to seek medical attention" (Davis *et al.*, 1990). Patients with chronic orchialgia are initially treated by non-surgical measures, and patients who fail to respond undergo surgical intervention. The various surgical procedures used have included epididymectomy, scrotal orchiectomy and inguinal orchiectomy, with failure to produce complete resolution of pain in 90%, 45% and 27% respectively (Davis *et al.*, 1990).

Vasovasostomy has been proposed as a treatment option for post-vasectomy pain. However, its undesirability and unacceptability on the grounds of defeating the primary purpose of the vasectomy is obvious. An unusually high success rate of epididymectomy in relieving pain in the post-vasectomy syndrome has been reported (Selikowitz and Schned, 1985) but this has not been borne out in our experience.

As a basis of the new surgical procedure which we describe, the anatomy of testicular innervation needs to be considered (Gee *et al.*, 1990). Pain sensation from the testis is subserved by sympathetic fibres with cell stations in the spinal cord at T10–L1 level. The fibres are conveyed via the aortic plexus, renal plexus and superior hypogastric plexus with contributions from the vesical and terminal periureteric plexuses. These fibres funnel down to be conveyed as the spermatic plexus along the spermatic cord structures. They finally innervate the testis, epididymis and vas deferens. The role of

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somatic innervation of the scrotum in the context of scrotal and testicular pain has been discussed by Yeates (1985). The genitofemoral nerve (L1, 2) has a retroperitoneal course and its genital branch traverses the inguinal canal on the outer surface of the cremaster. After supplying the cremaster itself, it perforates the cremaster and innervates the structures of the cord as well as the parietal and visceral layers of the tunica vaginalis. Stretching of the visceral layer of the tunica vaginalis by any testicular pathology causes pain felt in the testis via this pathway. The posterior scrotal nerves (S2,3) innervate a portion of the scrotum and there is clinical evidence to suggest that blockage of these nerves by local anaesthesia or a low spinal anaesthetic reduces the sensitivity and localisation of testicular pain on compression (Yeates, 1985). It is, however, at the level of the spermatic cord that the nerves usually concerned with the transmission of testicular pain are amenable to surgical extirpation by testicular denervation.

Patients and Methods

Between 1987 and February 1991, 4 patients underwent surgical treatment for intractable testicular pain, which we define as "incapacitating chronic testicular pain unrelieved by any modality of treatment". Our 4 patients fell into the category of intractable testicular pain following either epididymitis or vasectomy. All underwent clinical examination and relevant investigations to rule out any underlying problems and all were treated in the local pain clinic by a consultant anaesthetist. Failure of these measures or transient improvement led to testicular denervation as the treatment of choice.

Case Reports

Case 1. P.R., aged 32, underwent right scrotal exploration in 1986 with a clinical diagnosis of torsion of the right spermatic cord. Intra-operative diagnosis was acute epididymitis. He continued to have intractable right testicular pain afterwards. Repeated clinical examinations revealed tenderness of the right epididymis. Investigations, including mid-stream urine, intravenous urography and ultrasound scanning of the scrotum, yielded normal results. After failure of conservative measures, including spermatic cord and sympathetic blocks, the patient underwent a right testicular denervation in June 1987 with preservation of the vas deferens.

Case 2. J.C., aged 46, underwent bilateral vasectomy in 1976. He presented with intractable left testicular pain in 1987. Examination revealed a tender epididymis. Bacteriological investigations were unremarkable. An initial epididymectomy provided pain relief for 4 months and local anaesthetic sympathetic blocks provided transient relief for several months. Recurrence of pain led to a left testicular denervation in September 1989.

*Case 3.*G.C., aged 68, was seen in March 1990 with intractable right testicular pain of 1 year's duration. His urological history included recurrent attacks of "epididymitis" on the right leading to an ipsilateral vasectomy. Detailed assessment excluded bladder outflow obstruction, urinary tract infection and urolithiasis. Since local anaesthetic sympathetic blocks were unsuccessful in relieving the pain, a right testicular denervation was carried out in March 1990.

Case 4. P.W., aged 32, underwent bilateral vasectomy in June 1989. Following this he suffered from bilateral testicular pain and underwent a bilateral epididymectomy at a different hospital. This did not alleviate the pain and he was treated with a spermatic cord block and a lumbar sympathetic block. Assessment by a clinical psychologist favoured an organic basis for the pain. A right testicular denervation was performed in February 1991 and produced immediate relief of pain. A left-sided procedure is scheduled in the near future.

The procedure

The external oblique aponeurosis is incised through an inguinal incision and the spermatic cord mobilised. The procedure involves skeletonisation of the cord, leaving behind the testicular artery and 1 vein with or without the vas deferens. A Doppler probe is useful in identifying the testicular artery, which is very small and sometimes goes into spasm on handling. Using bipolar diathermy, the peri-adventitial layers of the artery are stripped over a length of 2 to 3 cm. The ilio-inguinal nerve is left undisturbed. The cremasteric fibres are divided completely and this results in a transection of the genital branch of the genitofemoral nerve. Haemostasis is achieved and the wound closed in layers.

Results

The immediate effectiveness of the operation was impressive. Patients woke up from anaesthesia reporting complete absence of testicular pain. At the time of this report, the follow-up periods in the 4 patients are 3 years, 2 years, 1 year and 2 months respectively. All patients are pain-free. Clinical examination revealed normal scrotal sensation and normal sized testes which were insensitive to pain. Colour Doppler ultrasound confirmed preservation of vascularity of the involved testes.

Discussion

The management of chronic testicular pain can be a frustrating experience both for the patient and the urologist. Post-vasectomy pain falls into this category. All patients with this problem should undergo a thorough clinical examination and relevant investigations to rule out associated conditions. Non-surgical management should include antibiotics, anti-inflammatory agents and referral to a pain clinic, as well as psychological evaluation in appropriate cases. Methods of treatment practised in the pain clinic include spermatic cord block, sympathetic block and transcutaneous electrical nerve stimulation. Patients who fail to respond to these measures will need surgical intervention. Epididymectomy has a high chance of success in the presence of sperm granulomas and other features of "Late post vasectomy syndrome" (Selikowitz and Schned, 1985). However, in the setting of chronic idiopathic orchialgia, epididymectomy has a high failure rate. Patients not responding to epididymectomy tend to be treated with orchiectomy. In this context, inguinal orchiectomy was found to yield better results than scrotal orchiectomy (Davis *et al*, 1990). In view of the destructive nature, unpredictable response, occurrence of phantom testicular pain in some (personal observations), and possible contralateral recurrence of pain, an orchiectomy should be avoided if at all possible. There is anecdotal evidence of cure of post-vasectomy pain with vasovasostomy, but this may not be an acceptable option.

We feel that a testicular denervation procedure should be offered to patients with chronic orchialgia who fail to respond to non-surgical measures. In this small series we found this operation to be extremely effective in relieving pain. Meticulous attention to dissection and gentle tissue handling should prevent the theoretical complications of haematomas and testicular devascularisation. Recurrent testicular pain following this procedure has not been encountered so far. Another theoretical possibility is the need for re-exploration of the inguinal area for a future herniorrhaphy, which could carry a risk of testicular devascularisation. Perhaps a preperitoneal repair would be the procedure of choice in such a situation. With our limited experience, we suggest that testicular denervation deserves a wider application in the treatment of intractable orchialgia.

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Testicular Prostheses: the Patient's Perception

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Summary—There is a paucity of data to determine if the insertion of a testicular prosthesis is effective in overcoming the psychological effects of an absent testis. A review of 25 patients who had had testicular prostheses showed a high overall level of satisfaction in the 19 patients who were traced. This satisfaction was subject to some qualification.

Testicular prostheses have been in use since 1941 (Girdansky and Newman, 1941) and in their present form since 1973 (Lattimer *et al.*, 1973). Their function is cosmetic and it is believed that they might alleviate the effects of orchiectomy. The incidence of psychological harm following the alteration of body image is unknown and only 2 studies have examined the psychological effects of loss of a testis (Money and Sollod, 1978; Weissbach *et al.*, 1983). Only one case report (Money and Sollod, 1978) attempts to assess whether the implantation of a prosthesis enhances the patient's body image. This study was performed to rectify this deficiency and to assess whether patients derived any benefit from the insertion of testicular prostheses.

Patients and Methods

The names of all patients who during the years 1981 to 1990 had a testicular prosthesis inserted under the care of one consultant (J.P.P.) were obtained from the operating theatre register. The average age of patients at the time of their original surgery, and the reasons for the absence of the testis, are shown in Table 1.

A postal questionnaire was sent to each patient, asking him to tick the most appropriate answer to 6 questions, and an appointment to attend the clinic was also offered for discussion of any matters arising from the questionnaire. The 6 questions were chosen to give some indication of how comfortable the patient was with his body image. Nineteen patients replied (76%) and only 2 attended for out-patient review. Efforts to contact the remaining 6 patients were repeatedly unsuccessful.

Table 1 Reasons for Insertion of Testicular Prostheses

Cause of loss	*No. of patients*	*No of prostheses*	*Average age*	
			Years	*(Range)*
Agenesis or maldescent	12	19	27.7	(17–35)
Cancer	3	6	31	(26–40)
Torsion	2	2	20	(16–34)
Iatrogenic	3	3	33.3	(22–40)
Trans-sexual	2	4	34.5	(28–41)
Miscellaneous	3	4	37.3	(28–53)
Total	25	38	29.8	(16–53)

Results

The questions and responses are shown in Table 2. Most of the respondents (15) were happy about their naked appearance in front of men and the majority (16) felt comfortable in non-intimate contact with women.

In more intimate encounters with women most of the patients expressed some reservations, only 9 said they felt confident and 3 avoided such circumstances, exhibiting the "bed-flight" response (Weissbach *et al.*, 1983). The majority also expressed the opinion that their appearance was only slightly improved or was unchanged, with 1

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dissatisfied patient (marked by an asterisk in Table 2) stating that he felt worse. This was the only patient who felt that the operation was not worthwhile; the others all felt that they would still wish to have the operation performed.

Discussion

Testicular prostheses have been available since 1941 (Girdansky and Newman, 1941) but their value in treating the adverse psychological effects of loss of a testis has been observed in only one case report (Money and Sollod, 1978). Indeed there has only been one study of the adverse psychological effects on which to base a requirement for use of an artificial replacement (Weissbach *et al.*, 1983). The incomplete response rate detracts from the overall value of the questionnaire, although all but one of the non-respondents had been seen in the outpatient clinic 6 weeks after their operation and were thought to be satisfied with the result of the surgery. One patient never attended for review. An attempt was made to contact all of the non-respondents and the failure to respond was due to inability to contact the patients.

The operation was considered worthwhile in 15 of 19 patients and it is of note that 18 would wish to have the operation repeated. Although this appears a very satisfactory outcome, it should be noted that 9 were less than confident when intimate with women and only 7 felt that their body image was greatly enhanced by the operation.

At first sight there would appear to be a discrepancy between the number of patients who were happy with their appearance in front of men and the small number who felt that their appearance had been improved by the operation. This difference can be explained by the fact that a number of patients had their implants inserted at the time of their original orchiectomy. Consequently their selection of responses of "unchanged" or "improved a bit" would have to be considered as being very positive reactions.

Only one patient was truly dissatisfied with the operation, especially as he continued to have "testicular" pain despite an orchiectomy. This patient had other features which distinguished him from the rest. He was a depressive and was married at the time of operation. This latter feature is unusual in men seeking a testicular prosthesis. However, neither of these features is unique to this patient.

It may have been expected that as these patients were self-selected, the outcome would have been

Table 2 Answers to Questionnaire

		Responses		
Questions	*Answers*	*A*	*B*	*C*
Would going to a public bath	A) Cause you no concern B) Worry you unless you could change privately C) Cause you such concern that you would not go	15	2	2
In female social company	A) You feel confident B) You avoid getting too close e.g. slow dances C) You feel self conscious	16	1	2
In intimate circumstances	A) You feel confident B) You feel uncomfortble but manage C) You worry so much that you avoid it	9	7	3
Is your appearance	A) Greatly enhanced B) Improved a bit C) Unchanged	7	7	5*
Was the operation	A) Worth all the pain B) Of only limited value C) Not worth it	15	3	1
If you lost your implant would you have it replaced	A) Yes B) No	18		1

* One said he was worse.

highly favourable to the use of the prostheses, but it can equally well be argued that the inherent deficit in each patient's ego that prompted him to seek a prosthesis in the first instance following the loss of a testis would never be completely cured by an operation. One patient attributed some of his lack of confidence to the slightly different texture of the prosthesis compared with the feel of his native testis and he thought he might be caught out in intimate circumstances when he felt he would be most vulnerable.

The conclusion to be drawn from this study is that patients who have lost a testis should be made aware that a cosmetic substitute is available. They will then be able to make their own informed decision on the desirability of such a replacement. It is unlikely, however, that this operation alone will be sufficient to restore a complete sense of normality for the patient.

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Results of the Surveillance Policy of Stage I Non-seminomatous Germ Cell Testicular Tumours

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Summary—A series of 115 patients with clinical Stage I non-seminomatous germ cell testicular tumours were managed with orchiectomy and close surveillance (median follow-up 36 months, range 3–119); 34 (29.5%) relapsed, 21 within 6 months, 29 within a year and the latest at 28 months. At relapse all patients were treated with platinum or analogue-based drug combinations, supplemented in 7 by retroperitoneal node dissection; 30 patients achieved durable remissions and 2 have had further relapses successfully treated. Two died; both had malignant teratoma intermediate with primary stage T1 and vascular and/or lymphatic invasion of primary tumour. At a median follow-up time of 36 months, the survivors (98.3%) demonstrate no evidence of disease, these results matching the outcome of other methods of management.

Vascular and/or lymphatic invasion was associated with an enhanced relapse rate but specific histology, T stage of the primary and pre-orchiectomy serum alpha-fetoprotein status did not appear to favour relapse. The first sign of relapse was tumour marker alone in 10 patients, radiological features alone in 12, or both in 10 patients. However, in 2 cases the relapse was first detected clinically. Furthermore, pre-orchiectomy and relapse marker status did not correlate well. These points emphasise the importance of all aspects of follow-up, none of which can be safely omitted.

Retroperitoneal node dissection (RPND) of patients with clinical Stage I non-seminomatous germ cell testicular tumours (NSGCTT) was common practice prior to 1980 and remains standard management in some areas of the world. Unquestionably, this technique gives the most accurate staging. In addition, patients shown to have Stage II disease by RPND are frequently cured by surgery, with or without supplemental chemotherapy. A report from the Sloan-Kettering Cancer Centre has claimed a 2-year disease-free survival rate of 92% in a cohort of 154 patients treated in this manner; this included a 96% 2-year disease-free survival rate for those shown to be pathological Stage I after surgery and an 88% 2-year disease-free survival rate for those who were identified as Stage II cases (Bredael *et al.*, 1983).

In spite of these very good surgical results, the need for RPND has been questioned and several groups have shown that many patients are cured by orchiectomy alone. This approach was first described by workers at the Royal Marsden Hospital, London (Peckham *et al.*, 1982). The availability of computed tomography (CT), the establishment of alpha-fetoprotein (AFP) and beta human chorionic gonadotrophin (beta-HCG) as reliable tumour markers and the development of effective chemotherapy capable of salvaging the relapsing cases, have made this approach realistic. This policy is common in New Zealand and a New Zealand register was established. We report this experience and attempt to define whether such a policy is effective and safe on a national basis. In addition,

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we have sought factors which may predict a propensity to relapse in any sub-set of patients.

Patients and Methods

A register of patients with clinical Stage I NSGCTT was established in Christchurch and participation from other centres was invited. The first patient was registered on 21 February 1980 and by 29 June 1990, the median follow-up of all patients was 36 months (range 3–119). In all, 115 patients were entered from 5 centres (Auckland 48, Christchurch 38, Dunedin 7, Palmerston North 11 and Wellington 11). Registration of patients usually occurred within 1 month of orchiectomy, this being the time required to complete the essential investigations and note the appropriate changes in the blood tumour markers. Once the decision to register was made, the patients' orchiectomy dates were regarded as their registration dates. Some of the patients from Auckland and Christchurch have been previously reported: 36 of the Auckland patients were studied by Thompson *et al.* (1988) and 16 of the Christchurch patients were included in the study by Raghavan *et al.* (1988).

To be eligible for this study, the patient had to have clinical Stage I NSGCTT and fulfil the following criteria: normal physical examination, chest X-ray (CXR) and CT scan of the chest, abdomen and pelvis. In addition, if the AFP or beta-HCG were raised prior to orchiectomy, these markers had to have fallen within normal limits, as appropriate to the half-life of each marker. Lymphangiograms were not performed. In addition, the patient had to be fully informed of the alternative treatments available and had to agree to participate.

All histological variants of NSGCTT, malignant teratoma intermediate (MTI), malignant teratoma undifferentiated (MTU), malignant teratoma trophoblastic (MTT) and teratoma differentiated (TD) were eligible. In addition, patients with pure seminoma (S) in which the beta-HCG was greater than 300 iu/L were included. Patients with primary T4 tumours and/or tumours in the cut end of cord were excluded. In the earlier part of the study, vascular/lymphatic invasion (VLI) was not consistently reported upon but has been so recorded for several years. In those cases in which this factor was not originally commented upon, a histological review has been obtained, wherever possible.

The protocol of surveillance required a clinical review, CXR and estimation of the beta-HCG and AFP at monthly intervals during the first year. This follow-up was done at 2-month intervals in the second year and at least every 4 months in the third year. In addition, each patient had a CT scan of the abdomen and pelvis at least every 3 months during the first year, every 4 months during the second year and as indicated thereafter. Follow-up after this time was at the discretion of the clinician, but most have continued with 6-monthly clinical reviews.

A number of variables including histology, extent of the primary tumour (T stage), presence or absence of abnormal levels of AFP prior to orchiectomy and presence or absence of VLI in the primary tumour have been noted and considered for statistical analysis. The chi-square test was deemed to be the most appropriate method for such statistical analysis and was employed for univariate comparisons. A multivariate logistic regression was attempted so that the influence of more than 1 variable could be evaluated simultaneously. However, as a consequence of the sparse cell numbers, this method of analysis was abandoned.

Results

The study group of 115 patients has been followed up prospectively on protocol for a median of 36 months (range 3–119). The median age of the patients was 28 years (range 18–77).

The histological diagnosis was MTI in 69, MTU in 32, MTT in 7, TD in 4 and S in 3 patients. In each of the 3 cases where the histology was reported as pure seminoma the beta-HCG exceeded 300 iu/L prior to orchiectomy. The primary tumour (T) stage was T1 in 100 cases, T2 in 11 and T3 in 4 cases. Serum AFP and/or beta-HCG were raised to abnormal levels prior to orchiectomy in 83 of 115 patients (72%). In the case of AFP alone, this tumour marker was elevated in 72 of 115 cases (63%). The presence or absence of VLI in the primary tumour was defined in 110 patients. Invasion was present in 47 (43%) and absent in 63 (57%). Vascular and/or lymphatic invasion were classified together as the majority of pathologists are not confident that they can clearly define whether the vessel involvement is vascular or lymphatic.

Relapse occurred in 34 of 115 patients (29.5%). Twenty-one of these relapses were noted within 6 months of registration, 29 within the first year and the remaining 5 at 13, 15, 17, 27 and 28 months respectively.

Two contralateral testicular seminomas were diagnosed at 17 and 20 months respectively. They have not been regarded as relapses and they have been considered as new primary tumours. Both of these patients were treated with orchiectomy and 1 also had abdominal node irradiation. At the time of follow-up, at 42 and 25 months respectively, both were currently free of disease.

The 34 relapsed patients were treated with platinum or platinum analogue-based drug combinations, supplemented in 7 cases with RPND, and 30 of these patients have achieved a durable remission. Two others have relapsed for a second time but are in remission again after further treatment. Two patients have died, both of whom had MTI histology, T1 primary staging and both had VLI. Their histories will be discussed in more detail.

The first of these patients relapsed in his spleen with no other disease evident. Splenectomy was followed by 4 cycles of chemotherapy including platinum, vinblastine and bleomycin. He achieved complete remission but relapsed 1 year later with hepatic metastases. He was treated with 4 courses of cisplatin and etoposide and a further 9 courses of etoposide but this treatment was unsuccessful and he succumbed. The second patient developed a solitary 1-cm pulmonary metastasis and was treated with 4 cycles of cisplatin and vinblastine and a complete remission was obtained. Three months after stopping treatment the nodule reappeared and was surgically excised, the specimen showing active disease. Two further cycles of cisplatin and etoposide were administered but he relapsed after 3 months when a CT scan revealed a 3-cm subcarinal mass which was treated with radiation with resolution. Six months later the disease relapsed in the subcarinal region and he was treated with combination chemotherapy including carboplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide. He achieved a clinical response but his markers did not return to normal. Within a year he developed meningeal and bone metastases for which palliative treatment was offered and he died of his disease.

Table 1 Site of First Evidence of Relapse

First feature of relapse	*No of patients*
Elevation of tumour marker alone	10
CT scan or CXR abnormal alone	12
Marker and radiology abnormal together	10
Clinical examination abnormal*	2
Total	34

*Supraclavicular fossa nodes 1
Splenomegaly 1

Table 2 Status of Tumour Markers

		Marker status on relapse	
		Positive	Negative
Pre-orchiectomy marker status	Positive	16	10
	Negative	4	4

The site of first evidence of relapse is illustrated in Table 1. It can be seen that the tumour markers were the first indication in 29.5% of cases and the scan or plain radiology in 35%; both of these parameters were abnormal simultaneously in another 29.5%. However, in 2 cases (6%), the first relapse was detected by clinical examination.

The status of the tumour markers at presentation and relapse is demonstrated in Table 2. In 20 cases the markers were consistent inasmuch as they were either abnormal or normal at presentation and relapse. On the other hand, in 14 patients this was not the case and in these patients the previously positive markers became negative at relapse or vice versa. In 1 patient the first 3 relapses were marker-negative but in the fourth, the AFP became abnormal.

The features found in the primary tumour that might predict relapse have been studied (Table 3). These include the presence or absence of vascular

Table 3 Relative Rates and Percentages of Relapsing Patients

Primary tumour	*Relapse rates (No relapse/no cases)*	*Relapse percentages (No relapse/no cases)*
Histology		
MTI	22/69	32%
MTU	8/32	25%
MTT	3/7	43%
TD	0/4	—
S	1/3	33%
T Stage		
T1	27/100	27%
T2	4/11	36%
T3	3/4	75%
AFP		
Raised	23/72	32%
Normal	11/43	26%
VLI		
Positive	20/47	43%
Negative	12/63*	19%

VLI = Vascular and/or lymphatic invasion
*$P = 0.0073$

or lymphatic neoplastic permeation in the primary tumour, the specific nature of the histology in the primary and the T stage of the primary. The AFP status in the patients' blood prior to orchiectomy has also been evaluated. Only VLI was shown to predict relapse ($P=0.0073$). Neither histological sub-type nor tumour stage was shown to be significant, though the small number of patients with MTT (3 relapses in 7 patients) and T3 primary tumours (3 relapses in 4 patients) prevented analysis to establish enough evidence for statistical significance.

It was realised that default of follow-up could have serious consequences and all patients were counselled prior to acceptance into the surveillance protocol. Only those who agreed to the protocol were registered. Notwithstanding this, 15 patients showed reluctance to attend clinics as recommended and some have defaulted completely. Often the default was relative and the patients have reported from time to time, or had blood tests or X-rays, but not necessarily attended the clinic. In some cases, follow-up information has been obtained via a third interested party. In this sub-set of 15 defaulters there were 2 relapses, 1 at 2 and another at 13 months. In both cases the relapse was dealt with satisfactorily.

Discussion

The acceptability of an active surveillance policy in the management of clinical Stage I NSGCTT depends upon its ability to produce results that are at least as good as the treatment it replaces. RPND, in the most skilled hands, gives excellent results. Donohue (1983) reported 100% long-term survival after such treatment in those clinical Stage I cases which were shown by RPND to be pathological Stage I cases, but the long-term survival in the sub-set identified as having pathological Stage II disease and who subsequently received adjuvant combination chemotherapy was 96.7%. Fung and Garnick (1988) reviewed the work of Donohue and 2 other groups and reported 99% long-term survival in 235 cases identified as pathological Stage I disease by RPND. On the other hand, in the 209 patients shown to be pathological Stage II cases at RPND and to whom adjuvant combination chemotherapy was given, the long-term survival rate was 94%. In the whole group of 444 patients with clinical Stage I disease prior to RPND, the long-term survival rate was 96.5%. If surveillance is to be compared with management by RPND and appropriate supplemental chemotherapy, it must match this excellent long-term survival rate. Our survival data do appear to match these results (98.3% survivors with no evidence of disease at 36 months median follow-up).

Some 75% of patients subjected to RPND are shown to be pathological Stage I cases and consequently undergo this surgery without any benefit. A significant number of such patients have, as a consequence of this operation, imperfect ejaculatory function. Despite minimal mortality and improved techniques in most surgical series, major surgery is not without significant short-term and sometimes long-term morbidity. Another treatment offered in the past to Stage I NSGCTT was adjuvant radiation of the retroperitoneal lymph nodes. This form of treatment is excellent in clinical Stage I seminoma but is less satisfactory in NSGCTT. In addition, it has an appreciable short- and long-term morbidity rate and, as with surgery, will result in the whole cohort of patients being treated when only about 25% really need such treatment. Another putative treatment would be adjuvant chemotherapy for all clinical Stage I cases, or possibly for those deemed to be at highest risk. One group has recommended 2 cycles of adjuvant chemotherapy for patients with neoplastic vascular invasion of the primary tumour. However, this did not eradicate relapse, as this occurred in 11% of their chemotherapy-treated cases (Pont *et al.*, 1990). In addition, such a policy would expose at least 75% of the cohort to unwarranted cytotoxic drugs. To compare favourably with these treatments, the surveillance policy would have to have less morbidity. Its morbidity rate in physical terms is certainly minimal, although it might be claimed that the prolonged follow-up requirements could be psychologically harmful. However, whatever mode of management is used initially (surgery, radiotherapy, short-course chemotherapy or surveillance) all patients will still be followed up at length. The advantage of surveillance is the absence of toxicity; certainly, the hazards of extensive abdominal surgery are no part of this management and possible long-term side effects of radiation or chemotherapy are also not seen, except in those who relapse and receive additional treatment.

Some workers recommend exclusion of patients with vascular invasion from surveillance policies as this decreases the relapse rate (Pont *et al.*, 1990). However, the same group also reports that adjuvant chemotherapy given to such excluded patients, whilst diminishing their relapse rate, does not entirely prevent relapse. We do not propose excluding patients with VLI from active surveillance but recommend that they be counselled as to the increased propensity of their sub-set to relapse. In such patients, the question of alternative treatments would arise and each patient should be treated on his merits. He may elect to have surveillance, lymph node dissection or adjuvant chemotherapy.

Non-compliance with loss of patients to follow-up is a worry to the clinicians participating in such programmes. However, non-compliance is also seen in patients who have been subjected to lymphadenectomy or radiotherapy as adjuvant treatment; thus this problem is common to all modes of management. In this particular study, some 15 patients (13%) defaulted to a greater or lesser degree. Informal follow-up in most of these has determined that they have not come to harm. Those who have relapsed do not seem to have suffered by their imperfect follow-up record, but numbers are small. Poor compliance in larger numbers of patients would almost certainly lead to a worse outcome for some patients.

Many clinicians involved in such a surveillance policy for clinical Stage I NSGCTT have speculated about the possibility of identifying sub-sets of patients with risk factors that would identify their propensity to relapse and might lead to early treatment by node dissection or possibly adjuvant chemotherapy. Most clinicans would not choose to include T4 primary stage patients in their surveillance policy and some also choose to exclude T3 cases. We have insufficient T3 patients in the current series to make any definitive observations, but 3 of 4 of them relapsed. Others have suggested that certain histological types, notably MTU, were more prone to relapse (Hoskin *et al.*, 1986) but this was not found in this series (Table 3). There were too few patients with MTT or seminoma with raised beta-HCG to reach definite conclusions about these sub-sets.

Other workers have suggested that the absence of raised serum AFP prior to orchiectomy is a factor predictive of relapse (Klepp *et al.*, 1990). It has been suggested that this would be a particularly useful prognostic factor as it avoids the variability inherent in histopathological reporting. This was not the case in our study as the presence or absence of a raised serum AFP prior to orchiectomy appears to offer no prognostic information (Table 3).

The only factor predicting a higher rate of relapse in the current study was VLI in the primary tumour (43% versus 19% ($P=0.0073$)). Other workers have reported this finding as the only factor of significance (Thompson *et al.*, 1988) or, in some cases, the most important of several factors (Hoskin *et al.*, 1986; Freedman *et al.*, 1987; Klepp *et al.*, 1990). The follow-up of the 36 patients documented by Thompson *et al.* (1988) is updated in the current report. Information on VLI must become part of the routine histopathological report as suggested by Klepp *et al.* (1990). It seems unlikely that more detailed histopathology reporting would be feasible or reliable for general adoption even if such features were confirmed by others as being of prognostic significance.

Another interesting feature that emerged from the present study was that although relapse was signalled in 29.5% of patients by elevation of a tumour marker, in 35% by abnormality in their radiology and in 29.5% by a combination of these, there were 2 patients whose relapse was signalled by a physical abnormality only apparent on clinical examination. Also, it is important to note that even patients in whom the pre-orchiectomy tumour markers were elevated need not necessarily demonstrate elevated markers in relapse. Conversely, those in whom the markers were normal before orchiectomy may relapse with abnormal markers. These observations emphasise that all elements of the surveillance protocol (clinical examination, tumour markers and radiology) are important and it is probable that none may be safely omitted, although others have advocated that CT scanning is not routinely necessary (Read *et al.*, 1983).

The current study reports upon the results achieved in a prospective surveillance study carried out on a national basis in New Zealand. The results appear to be equivalent to those achieved by such surveillance protocols carried out in single institutions and in the MRC collected series (Freedman *et al.*, 1987). They also appear to be as good as those achieved by those who advocate RPND in clinical Stage I cases (Bredael *et al.*, 1983; Klepp *et al.*, 1990) but avoid the necessity of major surgery in some 70% of the cohort.

In conclusion, we feel that a prospective surveillance policy for clinical Stage I NSGCTT cases is valid in a national setting but would emphasise that it is only possible when the participating centres have experienced clinicians, sophisticated radiology and access to accurate tumour marker evaluation.

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In vitro Investigations into the Formation and Dissolution of Infection-induced Catheter Encrustations

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Summary—Encrustations are the most frequent complications occurring with indwelling catheters and urine drainage systems. The conditions for bacterial infections, using synthetic urine and controlled contamination by *Proteus vulgaris*, were standardised by using an *in vitro* model. Crystal deposits on catheters were analysed by infra-red spectroscopy and scanning electron microscopy. The main components of deposits in all investigations were struvite ($MgNH_4PO_4.6H_2O$) 60–70% and carbonate apatite ($Ca_{10}(PO_4,CO_3)_6\ (OH,CO_3)_2$) 30–40%. Investigations as to the quality and quantity of encrustations confirmed the analysis. Irrigation treatment was carried out with physiological saline solution and citric acid solution (Suby G) to study and quantify the dissolution of crystal deposits. Regular irrigation with citric solution resulted in a 70% dissolution of encrustations and ensured free flow as ascertained by measuring flow rates.

Inadequate preventive measures with indwelling catheters and both open and closed urine drainage systems frequently lead to bacteriuria (Fincke and Friedland, 1976; Schaeffer, 1986). Encrustation of catheters is the most frequent complication of infections in the urinary tract (Dosch, 1969; Bruce *et al.*, 1974; Cox *et al.*, 1987). The crystal deposits lead to blockage of the internal lumen and enlargement of the external diameter. The qualitative composition of crystals formed corresponds to the composition of infection-induced stones and consists of struvite ($MgNH_4PO_4\ 6H_2O$) and carbonate apatite ($Ca_{10}(PO_4, CO_3)_6\ (OH,CO_3)_2$) (Hedelin *et al.*, 1984; Hesse and Schäfer, 1987; Hesse *et al.*, 1989). The cause of crystal formation lies in the splitting of urea by urease-forming bacteria (*Proteus, Providencia, Klebsiella* or *Pseudomonas* sp.) leading to alkaline urine with a high ammonia concentration. The conditions in urinary infections can be simulated in the *in vitro* model (Grenabo *et al.*, 1984; McLean *et al.*, 1985; Hedelin *et al.*, 1990). In previous investigations carried out at this Institute, human urine which was freshly collected each day was mixed with a bacterial suspension of *Proteus mirabilis*. The progress of encrustation of catheters was monitored in a circulation system. Owing to the changing composition of urine it was not possible to standardise this system and further investigations were made with synthetic urine. In addition, the concept of the *in vitro* bladder model was further developed.

Materials and Methods

Design of the in vitro bladder model

The apparatus makes the simulation of *in vivo* conditions of balloon catheter irrigation possible (Fig. 1). This apparatus consists of a double-walled glass cylinder (capacity 250 ml) circulated with water heated to body temperature (37.5°C). The opening at the base is closed with a silicon plug in which the balloon catheter (filled with 8 ml water) can be placed. The opening at the top is also closed with a silicon plug and fitted with 2 glass tubes, 1 to supply urine and 1 for sampling purposes.

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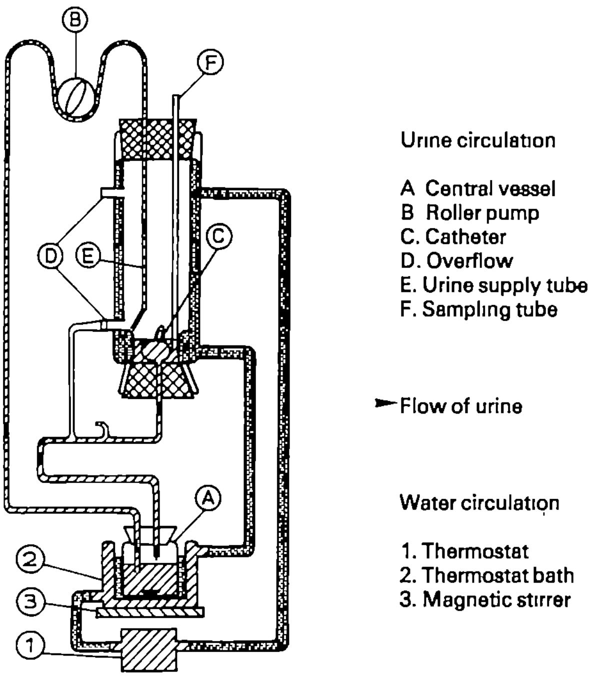

Fig. 1 Schematic concept of the *in vitro* bladder model.

Five sets of apparatus were connected in parallel for comparative investigations. The urine was collected in a central vessel and pumped through silicon-coated tubes. Fluid circulation was achieved through roller pumps (60–70 ml/h) and temperature was controlled by a thermostat. The urine was thoroughly mixed with a magnetic stirrer. Using balloon catheters with a catheter tip eye there was a residual volume of urine of approximately 20 ml, which corresponds to physiological conditions (Stickler *et al.*, 1987b). Each experimental cycle lasted 22.5 h/day over a period of 6 days. In various experimental cycles the catheter was irrigated with Suby G. Two litres of synthetic urine were freshly prepared each day, and a 2 ml bacterial suspension was also added and circulated around the catheters.

Composition of synthetic urine

The ion composition of synthetic urine had to be similar to the average for human urine. The synthetic urine described by Griffith *et al.* (1976) (Table) proved to be the most suitable. In the preparation of irrigation solution the entire equipment and the water had to be sterile to prevent spontaneous alkalinisation. The pH of freshly prepared synthetic urine was 6.45.

Bacterial suspension and bacterial counts

In order to simulate infection conditions a standardised bacterial suspension of *P. vulgaris* at a concentration of 10^6 cfu/ml was added to the synthetic urine. Bacterial growth was accelerated by adding 20 g/l trypticase soy broth. Based on previous tests, CLED (cystein lactose electrolyte deficient) and MacConkey cultures (Urotube ^{R} M, Hoffmann-La Roche, Grenzach) were used for semi-quantitative bacterial counts.

Catheter material

Sterile silicon-coated latex balloon catheters (18F) (Hoyer, Neuss) were used for all experiments. The balloon was inflated with 8 ml distilled water.

Irrigation fluids

Irrigation fluids included (1) a sterile physiological saline solution of 9 g ≙ 154 mmol sodium chloride/l and (2) citrate solution, pH 4.0 (Suby G^{R}, Vifor Medical AG, CH-Emmenbrücke): 32.3 g (154 mmol) citric acid monohydrate/l, 7.0 g (83 mmol) sodium hydrogen carbonate/l, 3.8 g (95 mmol) magnesium oxide/l and 0.1 g (0.269 mmol) sodium edetate/l. For irrigation purposes 100 ml of each fluid were added to the apparatus via the catheter and circulation was interrupted for 30 min.

Optimisation of test conditions

To obtain standardised conditions the experimental cycles were performed under various conditions, investigating pH values, ammonia formation (urease activity) and bacterial growth. A glass electrode was used for a potentiometric determination of pH; ammonia concentration was determined with an ion-selective electrode (Classen *et al.*, 1987).

Table Composition of Synthetic Urine

Compound	*g/l*
$CaCl_2 \cdot 2H_2O$	0.65
$MgCl_2 \cdot 6H_2O$	0.65
NaCl	4.60
Na_2SO_4	2.30
Na_2 oxalate	0.02
KH_2PO_4	2.80
KCl	1.60
NH_4Cl	1.00
Urea	25.00
Na_3 citrate	0.65
Creatinine	1.10
Trypticase soy broth	20.00

Preparation of catheters and analytical investigations

Cycles I–III were run as follows: Cycle I, no irrigation; Cycle II, daily irrigation of catheter with physiological saline solution; Cycle III, daily irrigation with citric acid solution (Suby G).

After completion of a 6-day cycle, the catheters were removed and suspended in a frame to dry at room temperature in a sheltered place.

After drying, a macroscopic and microscopic appraisal of the site, intensity and morphology of the catheter encrustations was carried out. To characterise the morphology of the encrustations, scanning electron microscopy was carried out after spraying the samples with silver. Scanning electron microscopy also allowed element analysis by the emission of radiation. Using infra-red spectroscopy, which had proved effective for stone analysis, the composition of catheter encrustations was analysed (Hesse and Sanders, 1988). The quantitative analysis of encrustrations was made after dissolution in 1 N hydrochloric acid. Crystals dissolved completely and a quantitative determination of calcium and magnesium was possible.

Flow rate in catheters

Flow rates were determined to measure the degree of catheter obstruction caused by crystal formation. The balloon catheter was turned upside down and was provided with a funnel. A clamp was fitted to control the flow of fluid. After filling the funnel with 50 ml of water the clamp was opened and flow rates were measured.

Results

Optimisation of test conditions

pH values Two hours after the test was started, pH values began a progressive rise (parallel measurements) After 10 h a pH level of 9.0 was reached and this remained constant (Fig. 2).

Urease activity. Continuous determination of ammonia throughout the experiments allowed the observation of urease activity at the same time. Ammonia concentration increased considerably after 4 h and reached a level of 600 mmol/l after 15 h. Subsequent variations were negligible (Fig. 3).

Bacterial counts. After contamination of synthetic urine with *P vulgaris* suspension, 1.0×10^6 cfu/ml were found after 15 min. In the following 10 h a progressive increase was observed up to a peak of 0.9×10^9 cfu/ml. After 13 h the bacterial concentration decreased, and returned to the original values after 21 h (Fig. 4). This development is attributed to the closed system, *i.e* micro-organisms died from a lack of nutrients in the second phase of the experiment.

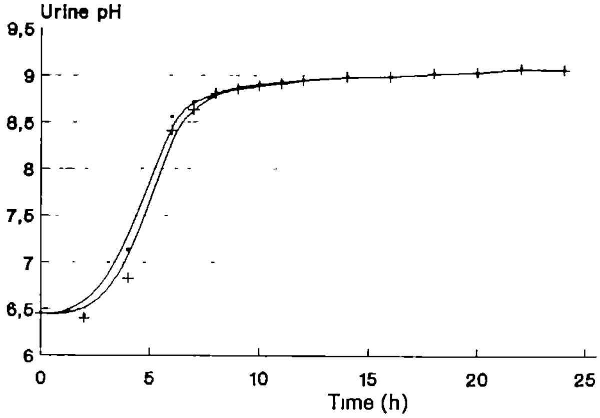

Fig. 2 Urine pH progress in 2 reactors throughout 1 test period

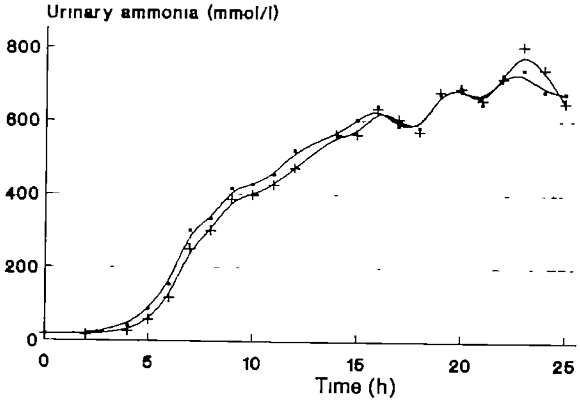

Fig. 3 Ammonia concentration in 2 reactors throughout 1 test period.

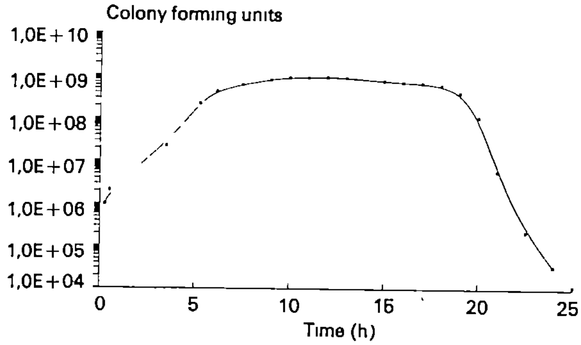

Fig. 4 *P vulgaris* counts throughout 1 test period

Macroscopic and scanning electron microscopic evaluation of catheter encrustations

Cycle I. Catheters without irrigation treatment showed major crystal deposits on the outer and

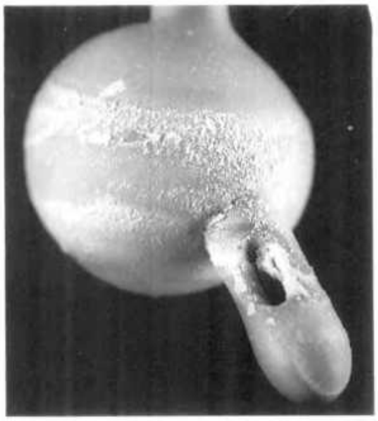

Fig. 5 Non-irrigated catheter.

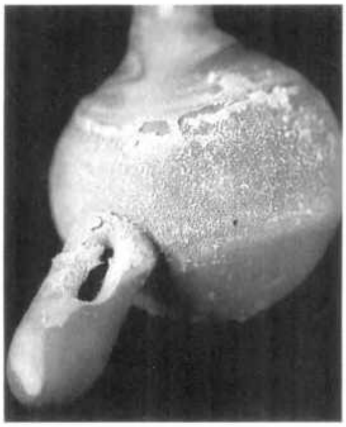

Fig. 6 Catheter after 6 cycles of irrigation with physiological saline solution.

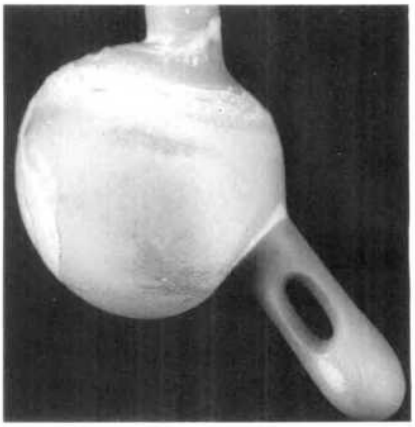

Fig. 7 Catheter after 6 cycles of irrigation with Suby G.

inner surface, eye and balloon (Fig. 5). Cycle II. Irrigation with physiological saline solution led to the mechanical removal of encrustations but substantial encrustations on the catheter eye and balloon were observed (Fig. 6). Cycle III. Daily irrigation with citric acid solution (Suby G) showed a catheter eye completely free of encrustations but slight residual encrustations on the dependent part of the catheter balloon (Fig. 7).

Scanning electron microscopic investigations showed minor fissures on the surface of a new catheter (Fig. 8). Catheters without irrigation treatment showed substantial encrustrations consisting of pseudo-amorphous carbonate apatite and very large struvite crystals (Fig. 9). The distribution of elements showed magnesium, calcium and phosphate. Spraying the samples with silver resulted in high silver peaks.

Quantitative infra-red spectroscopic analysis showed that the encrustations consisted of struvite (60–70%) and carbonate apatite (30–40%).

Quantitative determination of calcium and magnesium after dissolution with hydrochloric acid showed crystal deposits of 685 mg (100%) in catheters without irrigation treatment. After irrigation with physiological saline solution the percentage of crystal deposits was reduced to 62% and after irrigation with citric acid (Suby G) to as little as 27%.

The flow rate in untreated (new) catheters was 6.79 ± 0.23 s/50 ml ($n = 70$). Thus a rate of 7.00 s/50 ml was regarded as free flow. The following rates were observed in encrusted catheters: Cycle I, 15.86 s/50 ml; Cycle II, 8.66 s/50 ml; Cycle III, 6.47 s/50 ml.

Discussion

In order to allow quantitative analysis of encrustations on catheter surfaces, test conditions have to be standardised. Only when crystal deposits are reproducible can the effect of irrigation solution on dissolution processes be studied in detail. In our double-blind clinical studies a substantial decrease in catheter encrustations was achieved using Suby G solution (Bach *et al.*, 1990). Comparable results

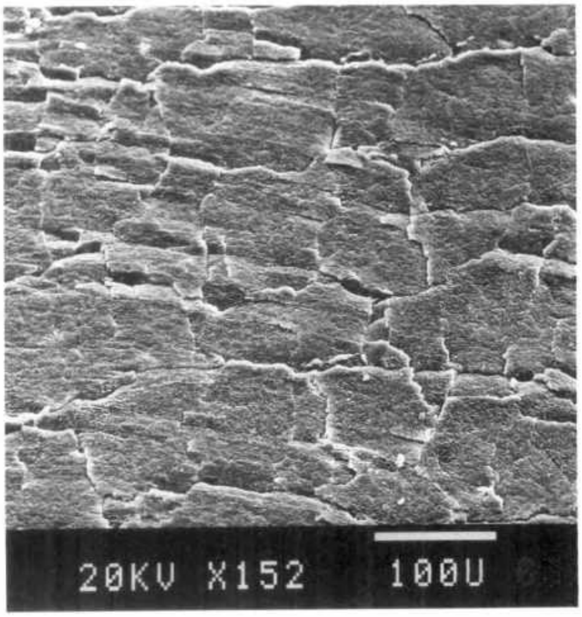

Fig. 8 Brand new catheter (outer surface). SEM, 152: fissures and tesselations on catheter surface.

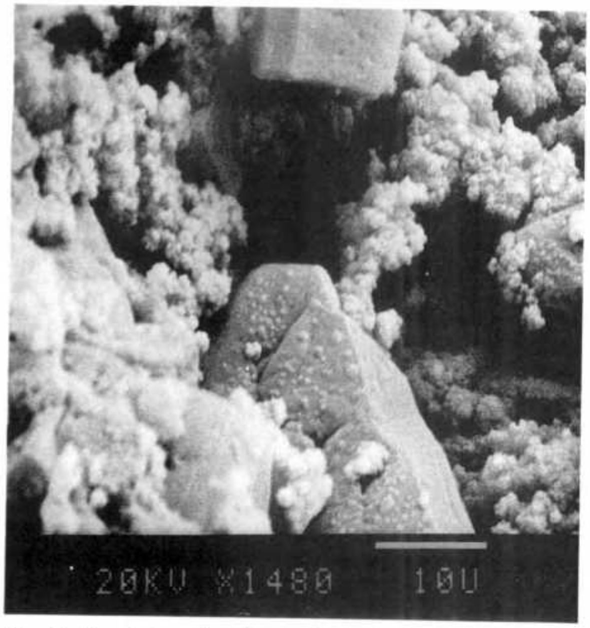

Fig. 9 Non-irrigated catheter (inner surface). SEM, 1480: struvite crystals with pseudo-amorphous carbonate apatite.

were achieved with human urine in experimental investigations (Hesse *et al.*, 1989). Given the differing ion concentration, pH values, buffer capacity and micro-organisms in each specimen of human urine, the use of synthetic urine was considered necessary. Griffith *et al.* (1976), Hedelin *et al.* (1985) and Cox *et al.* (1987) demonstrated that encrustations consisting of struvite and carbonate apatite formed in synthetic urine as well as in human urine. Griffith *et al.* (1976) and Hedelin *et al.* (1985) produced crystals on glass rods, whereas Cox *et al.* (1987) used pieces of catheter. In our experimental investigations with the *in vitro* bladder model (Fig. 1), conditions *in vivo* were largely simulated. The tip of the catheter pointed upwards and urine was supplied as depicted in Figure 1. The residual volume between the catheter eye and the bottom of the vessel was to 15–20 ml, which corresponds to conditions *in vivo*. Encrustations were reproduced with synthetic urine as described by Griffith *et al.* (1976). Synthetic urine was contaminated with *P. vulgaris*, providing higher urease activity than *P. mirabilis*, although the latter is known to occur more often in urethral infections (Griffith, 1978, Bach *et al.*, 1986). Hedelin *et al.* (1984) and Cox *et al.* (1988) described encrustations as a composition of calcium phosphate and struvite, with calcium phosphate as the major component. Hukins *et al.* (1983) and Griffith and Musher (1973) described struvite as the major component of encrustations. The latter was confirmed by our morphological investigations with scanning electron microscopy. Furthermore, the quantitative chemical determination of magnesium and calcium revealed a ratio of struvite: calcium phosphate of 2:1.

In our experience, the velocity of crystallisation and the crystallisation surface are responsible for the ratio of the 2 phosphates. Conditions of rapid development of infection favour the precipitation of pseudo-amorphic carbonate apatite. Carbonate apatite also proved to be the major component on the surface of the glass vessels used. The pseudo-amorphic character of carbonate apatite was investigated by scanning electron microscope. Carbonate apatite was also found in stones together with well developed struvite crystals (Hesse *et al.*, 1979). To achieve the dissolution of encrustations by irrigation, it is important to know their composition. Specific substances in the irrigation solutions can thus be employed for the formation of calcium and/or magnesium complexes. Physiological saline solution has not proved useful in the dissolution of obstructions caused by encrustations, as it had only a mechanical effect. Irrigation with citric acid solution (Suby G), on the other hand, led to a rate of dissolution exceeding 70%. Regular irrigation (and even double irrigation prior to removal of the encrusted catheter) always guaranteed a free lumen. Flow rates measured on indwelling catheters were then the same as on new catheters. Flow rates have proved to be a reliable indicator of encrustations on catheters (Kunin *et al.*, 1987). The efficacy of citric acid solutions for the dissolution of catheter encrustations was established by studies *in vivo* (Ruwald, 1983; Bach *et al.*, 1990) as well as by *in vitro* studies with human urine (Hesse *et al.*, 1989). The experimental studies made it possible to standardise test conditions and quantify test results.

There is controversy regarding the irrigation of indwelling catheters with a view to preventing urethral infections (Garibaldi, 1986; Stickler *et al.*, 1987a; Rao and Elliott, 1988). On the other hand, most assessments of irrigation treatment to reduce encrustations have been positive. Burns and Gauthier (1984) emphasised the necessity of keeping irrigation fluids in the bladder for an adequate period of time. Cools and van der Meer (1986) recommended that catheters be renewed as often as possible and that at the same time irrigation treatment be applied to dissolve obstructions.

Ruwald (1983) pointed out that irrigation is a costly and time-consuming treatment; nevertheless he admitted that such treatment leads to a decrease in the number of catheter blockages. Conti and Eutropius (1987) discussed the risk of bacterial infection in cases of repeated irrigation and referred to the advice of the CDC (Center for Diseases Control) to use irrigation only for the prevention or dissolution of obstructions. The use of modern antiseptic techniques during irrigation prevents bacterial infection to a large extent, which justifies the use of agents for dissolving encrustations. This method is a useful complement to other therapeutic methods—such as the promotion of diuresis, oral acidification and the inhibition of urease—in the reduction of catheter obstruction.

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Familial Hollow Visceral Myopathy with Varying Urological Manifestations

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Summary—A family with hereditary hollow visceral myopathy is described, with characteristic variation in expression between affected members. Very severe and widespread involvement of the gastrointestinal and urinary tracts in 1 patient contrasted with isolated urinary tract involvement in 2 others, and it is suggested that hollow visceral myopathy should be considered in the differential diagnosis of primary detrusor failure. The management of urinary tract involvement is discussed and a conservative approach is recommended.

A family is described whose members exhibit varying manifestations of chronic intestinal pseudo-obstruction and dilatational uropathy characteristic of hereditary hollow visceral myopathy, an inherited defect of smooth muscle which may cause atonic dilatation of any part of the gastrointestinal or urinary tract in the presence of normal innervation (Schuffler *et al.*, 1977). This is the twelfth such group identified (Anuras *et al.*, 1986; Fitzgibbons and Chandrasoma, 1987) with 4 affected members of 16 studied. In common with other groups, inheritance is thought to be via an autosomal dominant gene of variable penetrance, although affected individuals are not yet numerous enough to put this beyond doubt and no responsible gene or subcellular mechanism has yet been identified. A diffuse degenerative process involving smooth muscle has been implicated (Fitzgibbons and Chandrasoma, 1987). The commonest reported manifestation is megaduodenum, but any part or all of the gastrointestinal tract may be involved with or without associated urinary tract lesions. No biliary involvement has been described, nor has uterine dysfunction been shown to be a feature. A classification of the familial form of visceral myopathy has been suggested (Anuras *et al.*, 1986) but the patients described here, while fulfilling clinical and histological criteria of myopathy, do not fall within any of the categories defined.

Patients and Methods

The father (index case) and all 5 children (including cases 2, 3 and 4 who were full siblings) were interviewed about their medical history with specific reference to the gastrointestinal and urinary systems (Table). The 2 daughters were also asked about uterine dysfunction. Histories were obtained on the 9 third generation children aged 6 months to 4 years, none of whom is as yet affected. No information was available on the parents or siblings of the index case and there have been no infant mortalities in the group studied.

Case Reports

Case 1 was the most severely affected individual. He presented with a 20-year history of upper gastrointestinal symptoms including a laparotomy at 40 years of age at which a megaduodenum was found and a reduction duodenoplasty attempted. Over the following 20 years he had multiple admissions to hospital with subacute large bowel obstruction from megacolon unrelieved by laxatives or enemas and latterly the smooth muscle agonist Cisapride. During one of these admissions he was found to have chronic urinary retention with a 5-litre capacity bladder. Bladder neck incision followed by reduction cystoplasty failed to improve micturition and the patient was unable to tolerate self-catheterisation, so eventually

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Table Clinical Presentation and Pathological Findings in 4 Affected Individuals

Case	*Age (at presentation)*	*Presenting symptoms*	*Gastrointestinal symptoms*	*Urological symptoms*	*Investigations*	*Histology*
1	62♂ (51)	Abdominal pain, weight loss, haematuria	Gastric reflux, constipation, subacute obstruction	Retention, cystitis, pyelonephritis	Barium studies: adynamic oesophagus, megaduodenum, dilated small bowel, megacolon	Duodenum: thinned muscularis, normal myenteric plexus
					IVU: bilateral hydronephrosis, mega-ureter, megacystis	Bladder: chronic inflammation and fibrosis, normal myenteric plexus
2	31♀ (22)	Constipation	Constipation, gastric reflux	Recurrent infection since age 7	Barium meal oesophageal scarring, megaduodenum	None
					IVU: large post-micturition residue	
3	28♂ (21)	Loin pain	None	Childhood cystitis, enuresis until age 11	IVU: gross bilateral hydronephrosis and megaureter	None
4	33♂ (26)	Enuresis	None	Loin pain, enuresis	IVU: right ureteric reflux and hydroureter	None

urinary diversion was performed using double-barrelled cutaneous ureterostomies, the atonic ileum being unsuitable for conduit formation. The ureters drained poorly despite stenting with double-pigtail stents (Fig. 1). He continues to present with recurrent subacute intestinal obstruction and pyelonephritis.

Case 2 complained of gastro-oesophageal reflux and of constipation which required regular enemas and aperients to prevent faecal impaction. The radiological appearance of megaduodenum was characteristic (Fig. 2). She has had 2 children, both delivered at term by normal vaginal delivery.

Case 3 had repeated cystitis as a child and was enuretic until age 11. He had dilatation of the entire urinary tract at presentation and urodynamic studies showed the features of detrusor myopathy. This responded initially to phenoxybenzamine 10 mg *b.d* and double micturition, but deteriorating renal function and a large post-micturition residual volume necessitated the successful introduction of self-catheterisation at the age of 26. There was no evidence of gastrointestinal pathology.

Case 4 presented aged 26 years with a history of life-long enuresis and investigation revealed right-sided ureteric reflux with megaureter. The enuresis resolved 1 year after presentation without treatment. There was no history of gastrointestinal disturbance and the patient declined further investigation or follow-up.

Discussion

Hollow visceral myopathy is a rare condition which occurs as a sporadic or as a familial entity, and a severe infantile form has been identified (Schuffler *et al.*, 1988). The familial type has been classified into 3 groups (Anuras *et al.*, 1986). Patients in the first group have oesophageal aperistalsis, megaduodenum, redundant colon and megacystis thought to be transmitted by an autosomal dominant gene. Those in the second group have gastric atony and small bowel dilatation with multiple diverticula, thought to be autosomally recessive, whilst those in the third group show dilatation of the entire gastrointestinal tract without urological involvement, the transmission of which is not determined. The characteristic morphological finding is vacuolar degeneration and fibrosis of smooth muscle in the presence of apparently normal neural structures (Smith *et al.*, 1982). The severity and distribution of the myopathy vary considerably between family members.

The patients described here do not easily fall

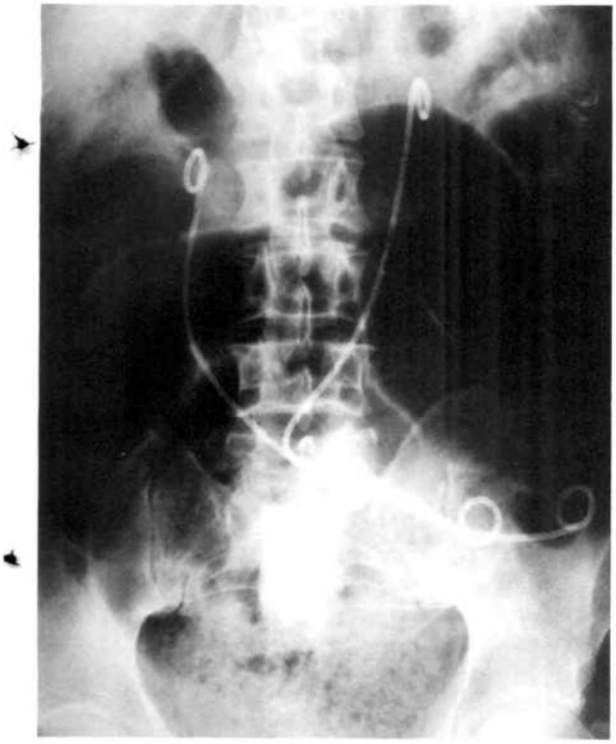

Fig. 1 Plain abdominal X-ray of case 1 with faecal impaction, small bowel dilatation and double-pigtail stents in urostomies.

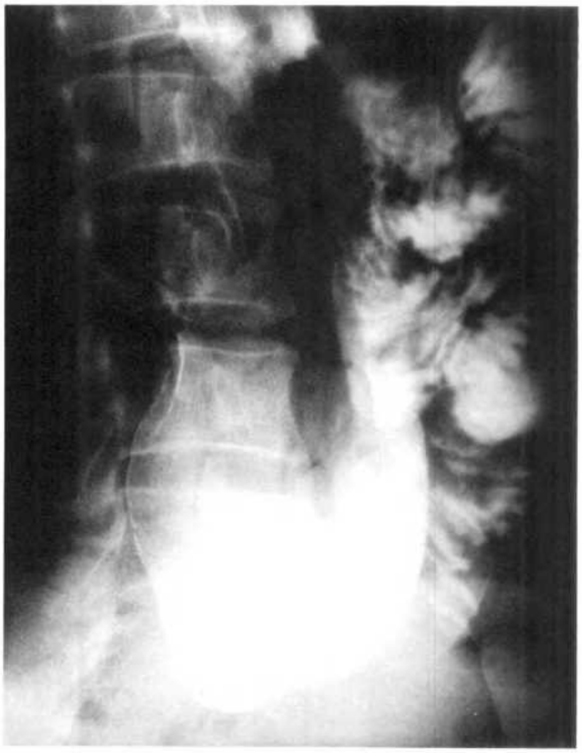

Fig. 2 Barium meal (oblique view) of case 2 showing characteristic megaduodenum.

within the categories defined above. The index case is the most extensively affected adult yet described (severe but very rare infantile forms are usually fatal by age 18 months) and cases 3 and 4 exhibit isolated urinary tract involvement which has been described only once before (Faulk *et al.*, 1978). In cases 3 and 4 the widespread gastrointestinal involvement which has been previously associated with urinary tract pathology has not developed, and although it is recognised that late development of pathology can occur we feel that these patients represent an expression of myopathy not accounted for by the present classification. It would seem that in the absence of an understanding of the disease process this classification has to be considered incomplete.

Reporting of urinary tract involvement in this type of myopathy has continued since the association of familial megaduodenum with megacystis was first noted (Law and Ten Eyck, 1962) with the commonest manifestation being megacystis presenting as urinary retention with recurrent infections. It is interesting to note that had case 3 presented in isolation, a diagnosis of primary detrusor failure would have been suggested and that of hollow visceral myopathy probably not considered. It is apparent that in other cases of primary detrusor failure a careful systems review and family history should be able to exclude hollow visceral myopathy from the differential diagnosis without invasive investigation being necessary (Bonsib *et al.*, 1984), since pathology does not seem to occur in the absence of symptoms.

The management of urological involvement in hollow visceral myopathy has not been widely discussed. The scanty literature on this rare condition contains claims of success in isolated cases with various surgical interventions (Law and Ten Eyck, 1962), including posterior wedge resection and V–Y plasty of the bladder neck relieving enuresis and ureteric reimplantation giving variable improvement in vesicoureteric reflux. However, most reports fail to give any details of management of complications of this myopathy and detailed follow-up is lacking. In this family the index case underwent several surgical procedures in an attempt to alleviate severe dilatational uropathy without success, and urological manifestations in other patients were successfully managed conservatively. Given the underlying pathology we believe that, in contrast to recommendations made in previous reports, surgery is unlikely to be successful in protecting renal function or in restoring normal micturition, and thus is not the treatment of choice in the management of urinary tract involvement in hereditary hollow visceral myopathy.

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PAEDIATRIC UROLOGY

Endoscopic Reappraisal of the Morphology of Congenital Obstruction of the Posterior Urethra

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Summary—Congenital obstruction of the posterior urethra was first systematically classified by Young in 1919. Since then, no-one has seriously challenged the presence of both Type I and Type III "valves", although the presence of Type II lesions has often been disputed. A review of Young's papers and more recent anatomical studies, together with endoscopic findings in our own patients, indicates that most congenital posterior urethral obstructions are anatomically similar. Consequently, Young's classification now seems redundant.

Hugh Hampton Young (Young *et al.*, 1919; Young and McKay, 1929) contributed greatly to the understanding and management of obstruction of the posterior urethra. He was the first to describe the endoscopic diagnosis of urethral "valves", and he developed a transurethral "punch" for treating the obstruction. He gave a great deal of detail in his reports on their first 21 patients. He included the presentation, treatment and findings in 15 children and adults. However, a number of factors militated against making a correct analysis of valve anatomy at that time. First, the 8 post mortem dissections opened the urethra through an anterior split (splitting the membrane). Second, 5 of the 8 lesions diagnosed endoscopically had prior urethral instrumentation, and third, all 8 endoscoped patients had the instrument introduced into the bladder before it was withdrawn to view the urethra. In the light of our recent findings these factors have a significant effect on the interpretation of the anatomy.

Two studies on the post mortem examination of patients with congenital obstruction of the posterior urethra (Presman, 1961; Robertson and Hayes, 1969) suggest that the original classification is incorrect. Presman presented 7 patients who died in infancy or early childhood and were usually managed by suprapubic urine drainage; 5 had a posterior urethral membrane. From 5622 West Indian autopsies in 15 years, Robertson and Hayes found 20 boys with urethral obstruction, 17 of whom had a posterior urethral membrane with a pin-hole meatus on the verumontanum. Their dissections involved removing the anterior wall of the posterior urethra without disturbing the obstructing membrane. Wigglesworth (1984) also showed specimens of a membranous obstruction as illustrated by Robertson and Hayes (1969) and Presman (1961).

We have observed the undisturbed anatomy of the posterior urethra while assessing the efficacy of the Whitaker diathermy hook (Whitaker and Sherwood, 1986) and we have recently commenced routine endoscopy of these boys prior to urethral instrumentation or valve disruption. This prospective study has involved the use of pre-operative suprapubic catheters and subsequent endoscopic video recording of entry into the urethra. All boys managed in this way were found to have a membranous obstruction with a pin-hole orifice adjacent to the verumontanum. Furthermore, insertion of a urethral catheter and the use of the diathermy hook convert these "Type III" membranes into Young "Type I" lesions. A retrospective review of 12 additional patients supports the view that congenital obstruction of the posterior urethra is similar in most boys.

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Patients and Methods

A series of 7 boys underwent cystourethroscopy specifically to assess the anatomy of their posterior urethral obstruction. These represent the last 7 cases of posterior urethral "valves" we have treated. In all, 5 had a suprapubic cystostomy for initial bladder drainage, 4 without prior urethral instrumentation.

Case Reports

Case 1. M.K. showed moderately severe obstructive uropathy from 18 weeks gestation on prenatal ultrasound (US). However, the amniotic fluid was normal. He was born at term with a palpable bladder. US was suggestive of urethral obstruction, so a suprapubic catheter was inserted after transfer to this hospital on day 2. On endoscopy a membrane obstruction was seen in the posterior urethra with a small defect posteriorly, consistent with the voiding cystourethrogram (VCU) findings. A Whitaker diathermy hook split the membrane to produce 2 firm edged "leaflets". A post-operative study showed a good result.

Case 2. J.W., the first born of twins, was noted to have bilateral hydronephrosis and a distended bladder at 36 weeks gestation. He was transferred for urological care within 24 h of birth when US confirmed the prenatal findings, leading to the insertion of a suprapubic catheter. An antegrade contrast study showed urethral obstruction, an abnormal bladder and left vesicoureteric reflux. At endoscopy a membranous obstruction was seen, with a posterior defect approximately the diameter of a 3F ureteric catheter (Fig. 1A). A Whitaker hook was used to disrupt the membrane, following which the sphincter could be seen coming to rest part way along the "leaflets" (Fig. 1B).

Case 3. G.H. presented for treatment on the first day of life, with a prenatal diagnosis of bilateral hydronephrosis which was first detected at 18 weeks gestation. He emptied his bladder during an attempt to insert a suprapubic catheter; a 6F feeding tube was therefore inserted to fill the bladder and facilitate the insertion of the suprapubic tube. A VCU showed posterior urethral obstruction and a filling defect in the membranous urethra. Endoscopy demonstrated a punctured syringocele and a posterior urethral membrane with a posterior midline defect adjacent to the verumontanum. A single passage of a Whitaker diathermy hook produced a "Type I" valve appearance.

Case 4. C.M. had a normal gestation and delivery, with 1 normal US at 16 weeks. Subsequently, he was noted to have haematuria during a febrile illness at the age of 3 weeks. Urinary infection was confirmed and US showed bilateral hydronephrosis and evidence of bladder outflow obstruction. He had a creatinine level of 185 mmol/l. A VCU via a suprapubic catheter showed obstruction of the posterior urethra (Fig. 2A). Endoscopy showed a urethral membrane with a posterior 3 mm defect (Fig. 2B). The membrane bulged markedly on bladder compression. The lesion was diathermied with a Bugbee electrode and 3 months later the remnants of the "valve leaflets" were resected. His renal function is moderately impaired.

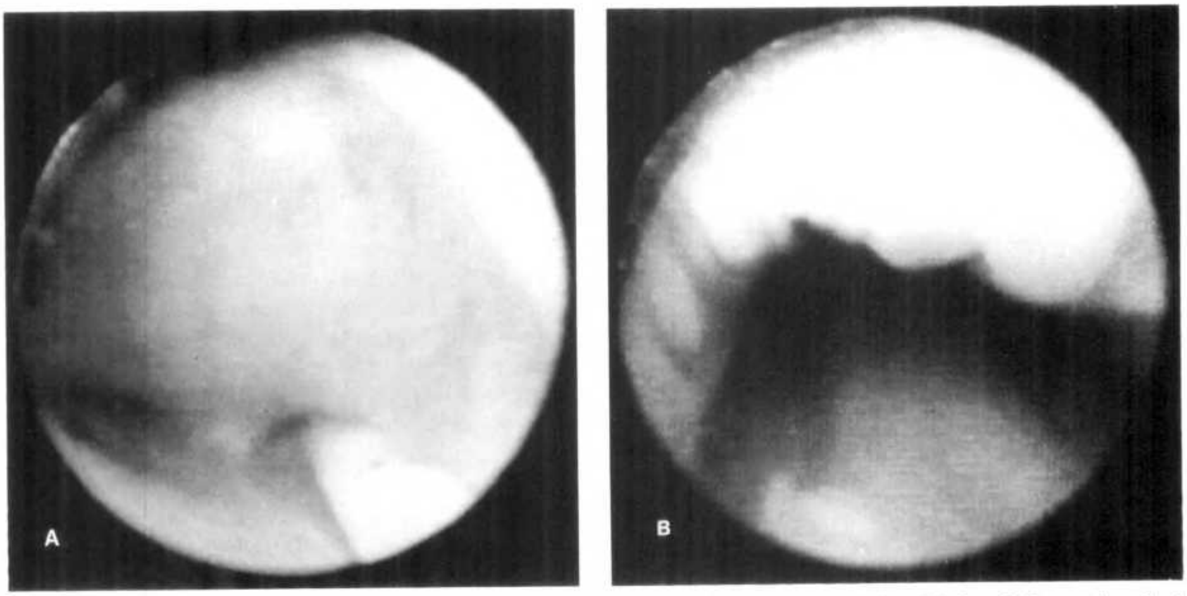

Fig. 1 (A) Case 2. Obstructing membrane with a 3F ureteric catheter through the posterior defect. (B) Case 2. External urethral sphincter above the membrane after passage of a Whitaker hook.

Case 5. T.H. was born after an uneventful full-term pregnancy and a normal vaginal delivery. He presented at 6 months of age with fever and irritability. The urine was assessed as part of screening for infection and after confirmation of a urine infection an ultrasound scan showed bilateral hydronephrosis and a thick-walled bladder. The urethra was also dilated. His renal function was normal. A suprapubic catheter was inserted followed by a VCU (Fig. 3A). Obstruction was confirmed and endoscopy was performed. After viewing the membrane, an 8F catheter was passed which split the obstruction into 2 "leaflets" (Fig. 3B). Because of the small size of the phallus the Whitaker diathermy hook was used to disrupt the membrane further; the "leaflets" were then more obvious and the sphincter could be seen to come to rest part way along these folds.

Case 6. O.F. was born at term from a normal pregnancy and delivery, including a normal US at 17 weeks gestation. He presented to us at 3 months of age, but first became unwell at 10 days of age. His episode of sepsis, at that time, was attributed to *Staphylococcus aureus* enterocolitis. Two urinary tract infections ensued 3 and 7 weeks later. Ultrasound then showed bilateral hydronephrosis and a thick-walled bladder. A VCU at the referring hospital demonstrated an abnormal bladder and posterior urethra. Unfortunately, no films were taken with the urethral catheter removed. Endoscopy was undertaken without further imaging or urethral catheter insertion. A membrane was seen attached to the verumontanum with a slightly larger defect than seen in the other index cases. The obstruction was resected with the infant resectoscope.

Case 7. J.H. presented at the age of 6 weeks following a grand mal convulsion secondary to renal failure and hyponatraemia. His bladder was drained for 2 days with a fine feeding tube and his creatinine decreased from 270 to 107 mmol/l. The patient was then transferred to this hospital, but not immediately to our care. US showed bilateral hydronephrosis, hydroureters, a thick-walled bladder and a dilated posterior urethra. A VCU was performed through a urethral catheter and cystourethroscopy was undertaken later the same day. An obstructing membrane was confirmed, with a pin-hole posterior orifice which was larger than in those boys above who had not had pre-operative urethral catheterisation; an 8F catheter partly split the membrane anteriorly. The Whitaker diathermy hook was used to disrupt the membrane further, which produced the 2 "leaflet" appearance of a "Type I valve". The sphincter was then visible lying on the "leaflets", between the verumontanum and the original membrane (as in Cases 2 and 5).

Before the introduction of our policy of suprapubic drainage without urethral instrumentation, 12 earlier patients had endoscopy at the time of a Whitaker hook procedure. This latter information has been collected retrospectively and is therefore less noteworthy than the cases presented in detail, but it does support the view that the obstruction of the posterior urethra is altered by the presence of an indwelling urethral catheter, or the passage of a urethral instrument as seen in the cases above.

All 12 boys had a urethral catheter for a contrast VCU and 11 had urine drainage via a urethral

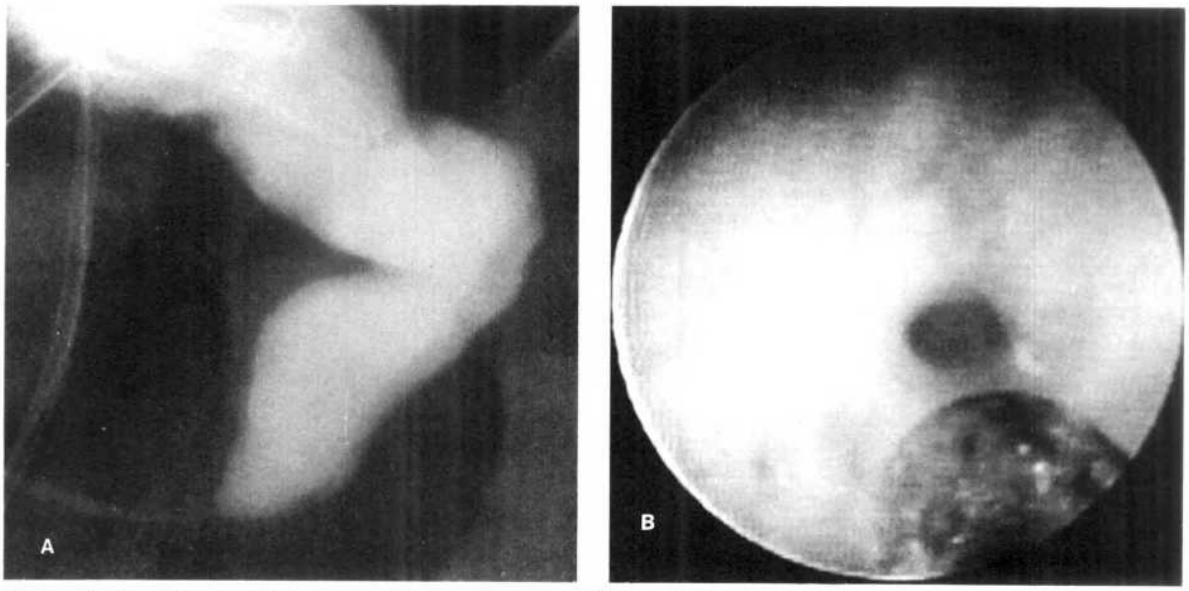

Fig. 2 (A) Case 4. Suprapubic cystogram showing obstruction of the posterior urethra. (B) Case 4. Typical membrane appearance is seen with a Bugbee electrode adjacent to the posterior defect.

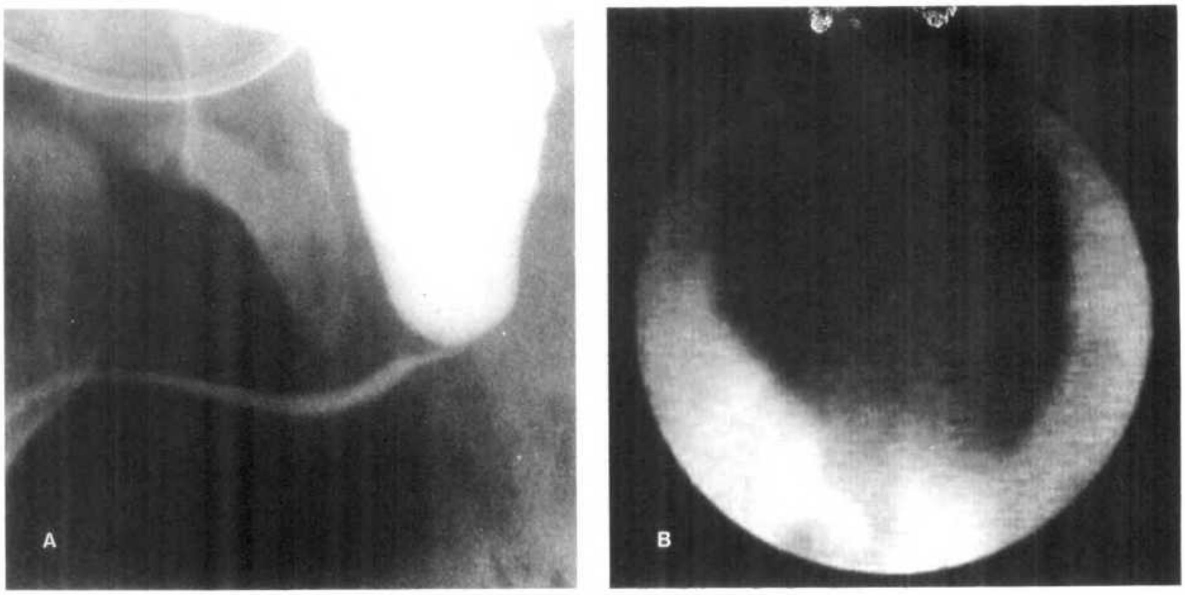

Fig. 3 (A) Case 5. Suprapubic cystogram showing the typical radiological appearance, with contrast entering the distal urethra via the posterior edge of the membranous obstruction. (B) Case 5. Membrane (as seen in Fig. 2B) has been converted to a "Type I" valve by a single passage of an 8F catheter.

catheter to allow stabilisation before their operation.

Nine of the 12 were labelled as "Type I valves", but all had had a urethral catheter *in situ* for a number of days, whereas 2 other boys with minimal manipulation of their urethra had an almost complete membrane, similar to those boys studied prospectively.

The last of the 12 had a "Type III obstruction" converted to "Type I valve leaflets" by the passage of the Whitaker hook. Pre-operatively this boy had only 1 day of urethral catheter urine drainage.

Discussion

Until Young made an endoscopic diagnosis, posterior urethral valves were identified either at autopsy (Morgagni, 1769; Tolmatschew, 1870; Commandeur, 1898; Knox and Sprunt, 1912) or by the passage of sounds (Bazy, 1903). Obviously, the latter did not help to elucidate the anatomy of urethral obstruction, but less apparent is the inaccuracy of the method used for post mortem dissection. Specimens illustrated in the early reports show that the urethra was opened by a midline anterior approach, leaving the posterior wall intact (Hinman and Kurtzmann, 1925; Kretschmer and Pierson, 1929; Stephens, 1963). This technique could easily split between 2 paramedian reinforcements of a membrane, a point which is well shown by the 2 diagrams in the report by Lederer (1911); a view from above shows a membranous obstruction, and later in the dissection (after an anterior midline incision) an anterior view shows a split membrane with 2 valve leaflets. Wilckens (1910) and Williams (1968) have similar anterior views in their publications.

By a different dissection method others have found an obstructing diaphragm. Jarjavay (1856) was the first to describe a membranous obstruction and Presman (1961) was the first to challenge the Young classification with a report of 7 boys, 5 of whom had a membranous diaphragm at the level of the verumontanum. All of his patients had died at an early age and most commonly had urine drainage via a suprapubic catheter. In 1969, Robertson and Hayes reported a series of 17 autopsies in which the posterior urethra was obstructed by an oblique membrane attached to the verumontanum posteriorly, with an adjacent pinhole orifice. Their dissections were performed by opening the bladder and then removing the anterior part of the posterior urethra down to the level of the obstruction. All of their cases had similar urethral pathology. Thus the method of dissection can affect the interpretation of the anatomy.

An analysis of the Johns Hopkins Hospital cases presented in 1929 by Young and McKay is of interest, remembering that the Young classification was based on their earlier report by Young *et al.* (1919). A total of 21 cases were reported (15 "Type I", 2 "Type II" and 4 "Type III"). Of these, 8 were cystoscoped (2 of these also had an autopsy), 8 were diagnosed by the antegrade or retrograde passage of a finger or the urethral "punch" (1 had a late autopsy). The remaining 5 patients had an autopsy only. None of the 4 patients with a "Type III" valve were diagnosed by endoscopy and only 1 was diagnosed at autopsy.

Of the 8 patients cystoscoped, 5 had had prior urethral manipulation, and from the operative reports the remaining 3 had the cystoscope passed into the bladder before visualisation of the urethra.

In the 1919 report only 3 of the 12 patients had been cystoscoped and they were 17, 26 and 42 years old.

Young *et al.* (1919) presented an extensive literature review which, unfortunately, does not indicate which of the cases were assigned to each part of the classification, thus precluding an accurate critical analysis. Analysis is also hampered by only 20 of the listed cases being included in the classification table, and the number of cases in the table and the text differ. Notably, patients as old as 85 years were included in the discussion.

Our 7 patients studied prospectively all had a membranous obstruction of the prostatic urethra immediately below the level of the verumontanum with a pin-hole meatus posteriorly. They were all similar in appearance, from below (Figs. 1A, 2B), to those shown from above by Lederer (1911) and Robertson and Hayes (1969). Midline reinforcements were documented in these patients, and conversion from the "Type III" to the "Type I" obstruction by the passage of a catheter and Whitaker diathermy hook was also seen (Fig. 3B). Our endoscopic pictures obtained before and after instrumentation are similar to the "Type III" and "Type I" pictures shown by King (1985).

Endoscopy has also shown the obstructing membrane to traverse the internal sphincter (Fig. 1B). This was well demonstrated in 3 of the prospectively studied patients and 3 of the reviewed group, but further observation is necessary before this point is verified.

As yet we have not documented the valve attachment as a "wind-sock" obstruction found by Field and Stephens (1974), but we have found significant, transient membrane ballooning when suprapubic pressure is applied. We postulate that a central defect is due to attempts at catheterisation, and is not part of the original pathology. Observation of non-instrumented "wind-sock" cases is necessary to clarify their anatomy.

The presence of a universal posterior urethral membranous obstruction makes the discussion of the different embryology for "Type I" and "Type III" lesions obsolete and accords with the embryological findings of Watson in 1922. He showed bands connecting the verumontanum with the anterior wall of the urethra in a 14-week fetus. Whether the obstruction is primarily an abnormality of the müllerian duct system or due to remnants of the urogenital membrane remains uncertain, but it is probable that one mechanism explains most cases.

From this review of Young's work, autopsy studies that have viewed the urethral obstruction from above, our prospective endoscopic study of 7 undisturbed or minimally disrupted urethras, and a retrospective analysis of 12 other boys treated in this hospital since 1987, it now appears that there is less variation in the nature of congenital obstruction of the posterior urethra than was previously recognised. The characteristics of the membrane appear as follows: (1) attachment posteriorly to the distal part of the verumontanum; (2) small hole adjacent to the verumontanum; (3) oblique attachment—distal anteriorly; (4) paramedian parallel reinforcements; (5) balloons distally; and (6) traverses the external sphincter.

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Case Reports

Paraplegia following Spinal Anaesthesia in a Patient with Prostatic Metastases

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Case Report

A 74-year-old man presented with a 4-week history of a poor stream. He also gave a 10-month history of low back pain radiating into both legs. Examination revealed a hard malignant prostate. Neurological examination revealed no loss of sensation in the lower limbs or around the anus. Radiographs showed multiple sclerotic deposits in the spine. He underwent bilateral orchiectomy and Tru-cut needle biopsy of the prostate under spinal anaesthesia with 2.5 ml heavy bupivacaine. The procedures were uneventful and a urinary catheter was left *in situ* Post-operatively he complained of tingling in his legs which was thought to be due to the spinal anaesthetic. The following day he was found to be paraplegic below the level of T12. Plain radiographs revealed loss of the T12 pedicles and partial collapse of the body. A myelogram was performed which revealed a complete block at the level of T12. A course of radiotherapy did not relieve his symptoms.

Comment

Neurological complications in spinal anaesthesia are rare, with an incidence of less than 1:10,000 (Phillips *et al.*, 1969; Kane, 1984). Only 2 previous cases of paraplegia following spinal anaesthesia in patients with spinal metastases have been reported (Kane, 1984). Surgeons performing operative procedures on patients with prostatic carcinoma should be aware of the possibility of paraplegia, since many such patients undergo spinal anaesthesia; 30% have spinal metastases at presentation and up to 80% have metastases at autopsy (Rubin *et al.*, 1974).

Our patient had no symptoms or signs of spinal cord compression pre-operatively, although he was known to have spinal metastases. It is unlikely that the injection of 2.5 ml bupivacaine into the subarachnoid space could have caused post-operative paraplegia. However, in the presence of tumour causing a block in the spinal canal the loss of cerebrospinal fluid during the tap may have caused the spinal cord to cone, leading to compression and paraplegia.

In the presence of spinal metastases a history suggesting spinal cord or cauda equina compression should be sought. Symptoms such as pain radiating into the legs and lower limb weakness are significant. A full neurological examination should be performed to exclude signs of spinal cord compression. This should include examination of peri-anal sensation and anal tone as well as lower limb power, reflexes and sensation. If there is any doubt about the possibility of incipient spinal cord compression a myelogram or MRI scan should be performed. General rather than spinal anaesthesia should be considered if there is a possibility of cord compromise.

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Carcinoma *in situ* following Tuberculous Cystitis: an Immunotherapeutic Dilemma?

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Intravesical Bacillus Calmette-Guérin (BCG) has gained increasing acceptance in the treatment of carcinoma *in situ* of the urinary bladder, with quoted 5-year tumour-free rates of up to 80% (Brosman, 1985). However, its mechanism of action involves the generation of an inflammatory reaction, the magnitude of which will depend in part on the patient's previous exposure to the tubercle bacillus (TB) or to BCG itself. Whether or not to administer BCG to a patient with a past history of TB presents an interesting dilemma.

Case Report

A 65-year-old lady presented with a brief history of painless haematuria. Other history of note was tuberculosis affecting the left kidney and bladder, for which she had received streptomycin therapy in 1963; this had resulted in a reduction in her functional bladder capacity.

Intravenous urography demonstrated a stone in the left kidney and scarring suggestive of old TB. Urine cytology was positive for malignant cells and cystoscopy revealed 3 large areas of carcinoma *in situ* (CIS) which were biopsied and treated with cystodiathermy. Subsequently an expectant policy was adopted with regular cystoscopic review. Cystoscopy at 3 months has shown further areas of CIS, again treated by cystodiathermy.

Comment

Irritative bladder symptoms develop in about 90% of patients during BCG therapy (Lamm *et al.*, 1985) as inevitable sequelae of its inflammatory mechanism of action. Patients who are purified protein derivative (PPD) skin test positive, either because of previous BCG vaccination or exposure to tuberculosis, seem to show a particularly favourable response (Badalament *et al.*, 1987), as their previously sensitised immune system is able to mount a more dramatic inflammatory reaction. There has been little consideration of the likely outcome of intravesical BCG administration to patients with a past history of urinary tract TB, but we feel that the local reaction may be so intense as to preclude its use, particularly in a patient with a reduced bladder capacity.

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Articular Complications of Intravesical BCG Treatment for Bladder Carcinoma

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Instillation of Bacillus Calmette-Guèrin (BCG) in the urinary bladder is now an accepted form of treatment for superficial bladder cancer (Morales, 1989). The optimal therapeutic regime has not yet been established, but results as good as (or better than) more traditional methods have led to an increasing number of patients being treated in this way (Martinez-Pineiro *et al.*, 1989). As with other treatments, increased use has increased the number and variety of complications (Lamm *et al.*, 1989); these vary from fever and cystitis to septic shock and death.

We present a patient who experienced complications after intravesical BCG prepared by the Dutch Institute for Public Health.

Case Report

A 48-year-old male presented with recurrent painful swelling of the left elbow. He had a history of right-sided pneumonia and left-sided pleuritis, probably of tuberculous origin, 20 years earlier. He underwent transurethral resection (TUR) of a solitary tumour (pTa GI) at the right ostium in July 1986. In October 1986, 3 small tumours were seen at the dome of the bladder, with positive cytology. Six weekly instillations of mitomycin were given. In December 1986 biopsy and fulguration of 3 small tumours were performed and mitomycin was continued at monthly intervals until June 1987.

The patient went abroad and TUR for 8 pTa GI–II tumours was performed in the United States in April 1988. Follow-up in August 1988 in this institution showed 2 tumours in the dome and BCG (RIVM) was started at weekly intervals. A tuberculin skin test at that time was negative In October 1988 the tumours were still present; biopsy and fulguration were repeated and the patient was placed on a monthly BCG instillation programme.

After the seventh month he complained of general malaise and fever (up to 38°C) of 1 week's duration. Physical examination was unremarkable. Laboratory tests were as follows: ESR 10 mm/h; haemoglobin 14.8 g/dl; white cell count 6.9×10^9/l; SGOT 41 u/l (normal <40); SGPT 83 u/l (normal <40); LDH 230 u/l (normal <220); alkaline phosphatase 166 (normal <100). A chest X-ray was unchanged

Treatment was discontinued. One month later arthritis of the left elbow developed and although this responded initially to conservative treatment, relapse occurred a few months later. X-ray revealed no articular destruction and laboratory tests, including liver function tests, showed no abnormality.

A synovial aspirate grew *Mycobacterium bovis* type BCG and anti-tuberculous triple therapy (rifampicin, isoniazid and ethambutol) was instituted. Neither ultrasound scan of the liver nor repeated chest X-rays demonstrated any pathology. Anti-tuberculous treatment was discontinued after 9 months and tomography of the left elbow revealed only a slight irregularity of the articular surface. The patient had no more articular complaints.

Comment

Side effects of BCG treatment are frequent, though symptoms are usually restricted to cystitis, haematuria and a flu-like syndrome with low grade fever and general malaise (Lamm *et al.*, 1989). Serious side effects such as pneumonitis and hepatitis are reported in 0.9% of cases (Lamm *et al.*, 1989). In hepatitis there may or may not be hepatomegaly and serum hepatic enzyme levels vary from normal to extremely raised. In biopsy-proven cases granulomas are usually non-caseating, although caseating granulomas have been reported. Cultures have been positive on rare occasions (Hunt *et al.*, 1973; Case Records of the Massachusetts General Hospital, 1975; Flippin *et al.*, 1980; Steg *et al.*, 1985; Israel-Biet *et al.*, 1987). In cases of pneumonitis the radiographic appearances also vary widely, with suspicion of inflammation being supported only by pathological findings of broncho-alveolar lavage in some cases (Israel-Biet *et al.*, 1987) and the radiological picture of miliary tuberculosis in others (Gupta *et al.*, 1988). Arthritic complications are regarded as an allergic manifestation of BCG therapy (Hughes *et al.*, 1989; Lamm *et al.*, 1989). The positive culture in our patient was probably the first evidence of mycobacterial spread. It is assumed that the combination of normal immune status in the patient and reduced virulence of the BCG organisms causes most cultures to be negative (Case Records of the Massachusetts General Hospital, 1975). Since there was no tomographic evidence of articular destruction in our patient, we considered this to be a case of tuberculous synovitis. The pathological findings indicate the potential gravity of the complications of BCG immunotherapy and the dangers of recurrent disease. We feel, therefore, that in cases of prolonged fever (up to 38°C for more than 24 h) following otherwise uncomplicated BCG instillation, "BCG-itis" should be suspected and further investigations undertaken. There is no consensus on the duration and intensity of prophylactic anti-tuberculous medication in such cases. In more severe cases we favour triple drug therapy (Brosman *et al.*, 1989) for 2 months, followed by double drug therapy (rifampicin, isoniazid) for 6 to 9 months.

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Renal Milk of Calcium—a New Contraindication to Extracorporeal Shock Wave Lithotripsy?

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Extracorporeal shock wave lithotripsy represents the most common and preferred mode of therapy for upper tract urinary calculi. Various recent advances have greatly limited the contraindications. We report a case of renal milk of calcium, a condition which we feel cannot be treated with lithotripsy.

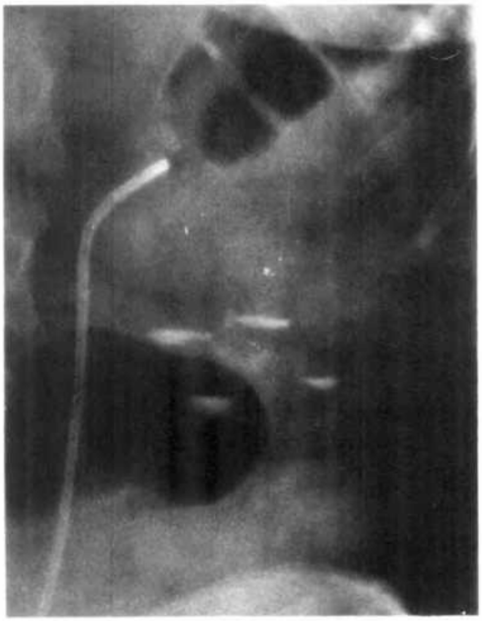

Fig. Erect film showing the change in the shape of the densities with characteristic "half-moon" configuration indicative of fluid levels.

Case Report

A 43-year-old asymptomatic female with a past history of right ureterolithotomy and left pyelolithotomy presented with a plain X-ray of the kidneys, ureter and bladder (KUB) revealing 3 calcific shadows over the left renal area. Intravenous urography confirmed that the calcific densities were within the dilated lower calyx. Diuretic renography demonstrated a non-obstructive pelviureteric junction. ESWL with a double pigtail stent was performed on a Siemen's Lithostar. The post-treatment KUB revealed no fragmentation but a change in the shape and size of the densities. ESWL was repeated 48 h later and the subsequent KUB showed only a single density without disintegration. ESWL was repeated 7 days later and the KUB again revealed 3 densities with no evidence of fragmentation. A critical review of the previous KUB films suggested changing shape, size and number of the densities but no fragmentation. An upright X-ray of the abdomen showed multiple fluid levels with a half-moon appearance which is diagnostic of renal milk of calcium. Sonography confirmed the postural movement of the opacities.

Comment

Milk of calcium is a semi-solid precipitate of calcium salts. It occurs occasionally in the biliary tract, less commonly in the urinary tract and rarely in the bronchogenic cyst. Howell (1959) was the first to report milk of calcium in a renal cyst. It probably forms because of incomplete egress of urine from an enclosed space. Usually asymptomatic, on a supine radiograph of the abdomen it appears as a faintly opaque density, often granular, with blurring or thinness of the calcification along the margins (Murray, 1971). The demonstration of a half-moon shaped opacity on erect or lateral decubitus roentgenograms is a diagnostic sign. On routine sonography, differentiation from calculus is difficult, but gravity-dependent sonography is the most sensitive method of diagnosis (Patriquin *et al.*, 1985). No treatment is indicated unless the condition is complicated by calculus formation or infection.

We suggest that a high degree of radiological suspicion on KUB can help in the diagnosis of this uncommon but important entity, thereby avoiding unwarranted ESWL therapy.

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Systemic Candidiasis caused by a Renal Transplant Ureteric Stent

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Double J stents have been associated with infective complications and although these have been well documented for the native ureter (Pocock *et al.*, 1986; Smedley *et al.*, 1988), little attention has been paid to the use of these devices in renal transplantation. In this situation the use of prolonged immunosuppression may lead to an increased risk of infective complications.

Case Report

A 53-year-old woman underwent cadaveric renal transplantation under immunosuppression with cyclosporin A and high dose steroids. Two months after transplantation the serum creatinine increased rapidly from a baseline of 211 μmol/l to a peak of 655 μmol/l and a transplant biopsy confirmed acute cellular rejection. This was treated with 3 daily doses of 0.5 g methylprednisolone given intravenously. At the same time the patient developed severe suprapubic pain and an antegrade pyelogram demonstrated a urinary leak at the vesicoureteric junction. This was treated by early exploration and the insertion of a double J stent (Surgitek, Wisconsin, USA). Further anti-rejection therapy proved necessary and a 10-day course of the monoclonal antibody OKT3 was administered. Ten weeks later routine urine culture yielded a heavy growth of *Candida albicans* and the ureteric stent was removed immediately using a flexible cystoscope. The patient subsequently complained of blurred vision and ophthalmoscopy revealed the presence of fungal balls in the right retina. A course of intravenous and intravitreous amphotericin B was successful but the patient sustained a marked loss of visual acuity in the right eye. It is suggested that whenever ureteric stents are used in renal transplantation they should be removed early in order to avoid infective complications.

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Profound Haemorrhage causing Acute Obstruction in Medullary Sponge Kidney

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Case Report

A 45-year-old woman was admitted with a 2-week history of persistent haematuria. She had suffered 2 previous episodes of haematuria and an intravenous urogram had demonstrated the typical features of bilateral medullary sponge kidneys (MSK). On admission she was tender in the left loin but apyrexial. Over the following 24 h she became increasingly unwell; she developed a pyrexia, severe left loin pain and increasing haematuria which required transfusion. A significant *Escherichia coli* urinary infection was found. Intravenous urography demonstrated marked delay in the elimination of contrast from the left kidney, with a dilated pelvicaliceal system. Parenteral antibiotics were commenced and under local anaesthesia a 7 F percutaneous pigtail catheter was inserted, with initial drainage of blood. The immediate antegrade nephrostogram demonstrated a filling defect at the pelviureteric junction and upper ureter (Fig.) The patient's condition improved and on the following day a 9.5 F rigid ureteroscope was passed up the left ureter. This revealed a large clot in the renal pelvis. Agitation with a guide wire broke up the clot, which was then flushed out through the nephrostomy tube by the ureteroscopic irrigant. The patient made a full recovery and a further nephrostogram demonstrated free flow of contrast down the ureter. Blood clotting studies were normal.

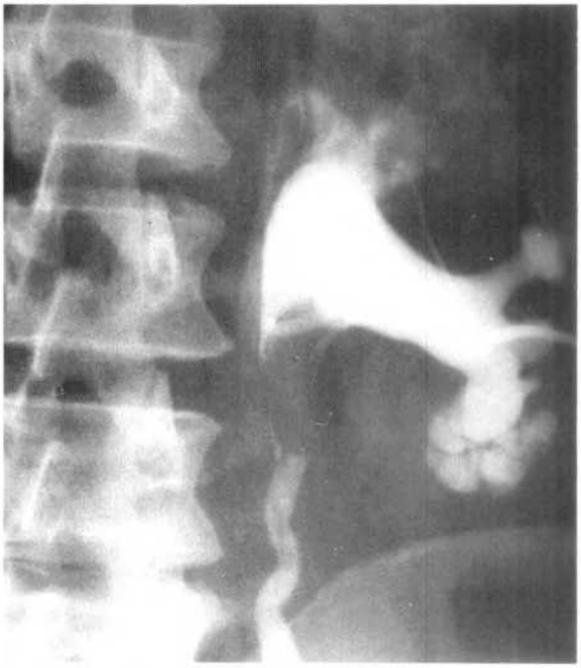

Fig. Immediate antegrade nephrostogram showing obstructing filling defect in the renal pelvis, appearances consistent with clot.

Comment

Although medullary sponge kidney is usually regarded as a relatively benign congenital condition, the prognosis is poor in 10% of patients. The condition is usually bilateral and renal failure may result from recurrent infection and/or stone formation (Kuiper, 1976). Approximately 30% of patients have haematuria, occasionally heavy (Kuiper, 1976). Haemorrhage can be severe enough to require surgical control, occasionally by nephrectomy (Ram and Chisholm, 1976).

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Urethro-vaso-cutaneous Fistula: an Unusual Complication following Bladder Neck Incision

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Case Report

A 61-year-old man with a 1-year history of recurrent urinary tract infection underwent elective cystourethroscopy under general anaesthesia. A tight bladder neck was observed and rectal examination revealed a small benign-feeling prostate. A Turner-Warwick type bladder neck incision (Turner-Warwick and Whiteside, 1982) was carried out at 7 o'clock posteriorly and he made an uneventful recovery. Post-operatively, his urinary flow rate was much improved and his MSU was sterile. At routine out-patient follow-up 2 months later, he continued to remain asymptomatic and was discharged from further follow-up.

He returned to the urology out-patient clinic 2 years later through referral by his general practitioner with a diagnosis of bilateral epididymo-orchitis which had failed to respond to 2 courses of antibiotics. On further enquiry, he described mild orchitis on and off for 2 years which had been treated by his general practitioner. Examination revealed a markedly enlarged tender right testis and a left testis of normal size. He was treated with parenteral antibiotics and subsequently a right orchiectomy was performed. Histology of the testis confirmed acute epididymo-orchitis.

A few weeks after his discharge the patient re-presented with leakage of urine via the right side of the scrotum during micturition. Inspection of his genitalia confirmed a demonstrable urine discharge from a small opening at the lateral end of his right scrotal scar. A micturating cystogram (Fig.) showed bilateral urethro-vasal and seminal vesicle reflux with leakage of contrast medium through a right urethro-vaso-cutaneous fistula. The patient was offered either temporary urethral catheterisation or right vasectomy but declined. On review 2 months later the fistula had resolved spontaneously.

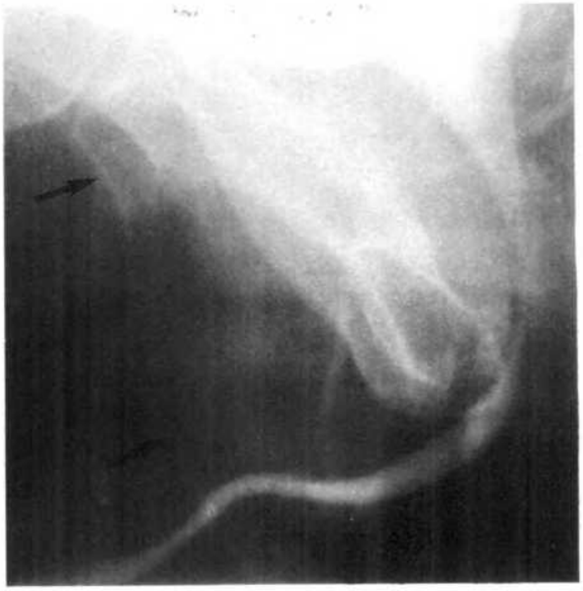

Fig. Micturating cystogram showing free bilateral urethro-vasal reflux and a right urethro-vaso-cutaneous fistula (with leakage of contrast on to the scrotal skin).

Comment

Scrotal fistulas may arise from surgery for hypospadias (Shapiro, 1984), after implantation of a testicular prosthesis, scrotal injury (Yasumoto *et al.*, 1984), renal transplantation (Noel and Velchik, 1986), complicating paraplegia (Ahn *et al.*, 1989), xanthogranulomatous pyelonephritis (Calvo-Quintero *et al.*, 1989) or hidradenitis suppurativa of the scrotum (Buckley and Sarkeny, 1989). These fistulae seldom involve the vas deferens or urethra except in the case of paraplegic patients. In recurrent epididymo-orchitis, urethro-vasal reflux is sometimes incriminated as the underlying cause and vasectomy has been advocated as the appropriate treatment to prevent reflux. Desai and Abrams (1986) reported a single case of vasal urinary fistula after vasectomy.

The patient reported here underwent an uneventful bladder neck incision with marked improvement of his symptoms. The development of unresolved epididymo-orchitis 2 years later was also treated promptly by surgical excision and antibiotics. In view of the bilateral urethro-vasal reflux as well as free reflux into the seminal vesicles, with a history of recurrent orchitis since the operation, it seems likely that the reflux resulted from the bladder neck incision. The incision might have damaged the "antireflux mechanism" at the ejaculatory duct level, increasing the susceptibility to recurrent bacterial orchitis. Although high pressure bladder outflow obstruction may cause or contribute to the reflux, the exact aetiology of the formation of the fistula subsequent to the orchiectomy remains unknown, since the fistula disappeared spontaneously and the patient remained unobstructed.

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Requests for reprints to: S. Liu, Department of Urology, St Batholomew's Hospital, West Smithfield, London EC1A 7BE.

Severe Allergic Reaction to an Intra-urethral Preparation Containing Chlorhexidine

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A patient developed a severe anaphylactic reaction after the repeated use of a catheter gel. An allergic reaction to the chlorhexidine component of the gel was recognised only after skin tests. Surgeons and anaesthesiologists should be aware of this possibility when an anaphylactic reaction occurs during or immediately after operations on the genitourinary tract.

Although chlorhexidine is widely used as a medical disinfectant, reports of adverse reactions are rare. Reactions include delayed-type contact hypersensitivity (type IV allergy) and reactions of the immediate type (type I allergy). Both types of reaction may occur in the same patient (Bergqvist-Karlsson, 1988; Okana *et al.*, 1989; Susitaival and Häkkinen, 1989). We report a patient who developed anaphylactic reactions on 3 occasions immediately after the use of a catheter gel for cystoscopy.

Case Report

A 61-year-old man was admitted with obstruction of the prostate and recurrent bladder stone formation, after transurethral resection (TUR) of the prostate 10 years previously. In 1985 he underwent a myocardial revascularisation. He used no medication.

The patient was premedicated with morphine-sulphate 10 mg and haloperidol 5 mg intramuscularly. Initial blood pressure was 170/100 mmHg and pulse 70/min. Following pre-oxygenation, anaesthesia was induced with thiopental 500 mg, fentanyl 200 mg and vecuronium 8 mg to facilitate intubation. After oral tracheal intubation the patient was ventilated with a mixture of O_2/N_2O (3/6 L/min). Anaesthesia was maintained with isoflurane 0.5%. The duration of anaesthesia was 30 min and the operation was uneventful. Rest curarisation was reversed with atropine 0.5 mg and neostigmine 1.5 mg intravenously. Immediately after this the blood pressure dropped severely, the patient became red and oedematous all over the body, insufflation pressure increased and rales were heard over the chest on auscultation. The surgeon, who had just put a catheter into the bladder, denied giving anything special to the patient, so an allergic reaction to medication, probably atropine, was assumed. Resuscitation was started immediately. Ephedrine 25 mg, calcium gluconate 1 g, hydrocortisone 2 × 200 mg, NaCl 0.9% 500 ml and Haemaccel 500 ml were administered without an adequate increase in blood pressure. Finally, the administration of 0.4 mg epinephrine resulted in an increase in blood pressure to 80/50 mmHg.

To clarify the haemodynamic situation a Swan Ganz catheter was inserted. The pulmonary pressure (PP) was 45/10 mmHg and central venous pressure (CVP) 14 mmHg. After starting a continuous infusion of dopamine 6 mg/kg/h and nitroglycerine the patient was transferred to the Intensive Care Unit. During the next 12 h further recovery was observed. The arterial blood pressure was 100/40 mmHg, CVP 6 mmHg, PP 24/12 mmHg, cardiac output 8L/min with a total peripheral resistance of 580 dyn s/cm-5 and a urine production of 1750 ml.

Dopamine and nitroglycerine were stopped within 15 h and the patient left the Intensive Care Unit in good condition.

The post-operative period was uneventful. However, 3 and 4 months after the operation simular reactions followed cystoscopy performed because of haematuria; the second cystoscopy was followed by a severe anaphylactic reaction. These reactions occurred immediately after cystoscopy without any other possible causes and alerted us to the possibility that they could be caused by the catheter gel (Instillagel) The same gel had been used immediately after the operation.

Instillagel is a local disinfectant with anaesthetic properties. It contains the following ingredients: 2% lignocaine hydrochloride, 0.05% chlorhexidine digluconate, 0.06% methylparaben and 0.025% propylparaben. An allergic examination with the gel and the separate ingredients was performed (Table).

Anaphylactic reactions after local use of chlorhexidine are rare and only 15 cases have been reported in the literature. Between 1967 and 1984 about 50 cases of adverse reactions to chlorhexidine gluconate were reported (Okana *et al.*, 1989). These included 22 patients with a fall in blood pressure, 13 with dyspnoea, 4 with cyanosis and 9 with anaphylactic shock. It was recommended that chlorhexidine gluconate should not be used on mucous membranes.

Table Results of Skin Tests

Epicutaneous tests			
Substances (read at)	20 min	48 h	72 h
I C D R G.* standard series a/b/c			
a. European standard	—	—	—
b. Antimicrobials, preservatives	—	—	—
c. local anaesthetics	—	—	—
Instillagel	—	—	—
Installagel after skin-stripping	—	—	—
Scratch tests			
NaCl 0 9% cg	—		
Histamine 0.1% saline	+ +		
Chlorhexidine digluconate 0.05%	+ + **	—	—
Chlorhexidine digluconate 0.05% in control person without history of allergy	—	—	—
Atropine 1 · 1000/1 · 100/1 : 10/1 : 1/	—		
Lignocaine hydrochloride 2%	—		
Intracutaneous tests			
Atropine 1 : 1000/1 : 100/1 : 10/1 : 1	—		
Lignocaine hydrochloride 2%	—		

*I.C.D R.G International Contact Dermatitis Research Group.

**Wheal and induration 10 × 10 mm, together with burning feeling of tongue and mouth

In our patient, an anaphylactic reaction to chlorhexidine was not taken into account initially and he had 2 more anaphylactic reactions before this possibility was considered and finally proven by skin tests. Recently a severe allergic reaction followed the use of Instillagel (Carr, 1990) and was thought to be due to the parabens preservatives. A severe anaphylactic reaction to methylparaben after using a rectal lubricating jelly was reported by Jones (1988). Anaphylactic reactions occurring during surgery can easily be interpreted as reactions due to anaesthetics, for example atropine (Aquilera *et al.*, 1988), fentanyl or thiopental (Doenicke and Koenig, 1983; Ring, 1987). More awareness of possible adverse reactions after using chlorhexidine on the skin and mucous membranes will contribute to early recognition of the danger to the patient.

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British Journal of Urology (1992), **70**, 453–457

Points of Technique

Upper Quadrant End Ureterostomy as Urinary Diversion for a Solitary Kidney in a Case of Extensive Urothelial Tumours

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Department of Urology, East Birmingham Hospital, Birmingham

A 66-year-old retired development engineer who worked in the tyre industry from 1946 to 1960 had been exposed to beta-naphthylamine, the well established industrial carcinogen. He first presented in 1980 with a sessile 4-cm (pT1G2) transitional cell tumour of the bladder with normal upper urinary tracts. This was resected endoscopically and subsequent frequent recurrences were similarly treated at regular intervals with no change in histological grade. A course of intravesical thiotepa was given in 1984 for recurrent superficial tumours and a repeat intravenous urogram (IVU) later on that year was normal. However, in 1989 he presented with right renal colic in the interval between cystoscopies. An IVU revealed a non-functioning right kidney and multiple tumours in a dilated left renal pelvis and in the urinary bladder (Fig. 1). Further investigations by ultrasound and CT scan showed that the right upper urinary tract was grossly dilated and filled with tumours and clots. Isotope renography confirmed absent right renal function. His serum urea and creatinine were normal, maintained by the left kidney despite the multiple renal pelvic tumours and a stricture below the pelviureteric junction. The left ureter was dilated but free of tumour.

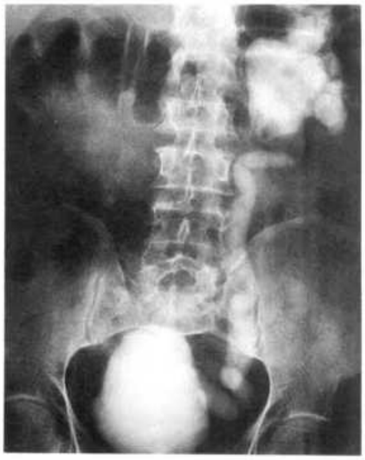
Fig. 1 IVU showing non-functioning right kidney, left hydroureteronephrosis and multiple urothelial tumours within the left pelvicaliceal system and the urinary bladder.

A right nephroureterectomy was performed and followed by a second-stage cystoprostatectomy with a left upper quadrant terminal cutaneous ureterstomy (Fig. 2). The ureter was delivered through the retroperitoneum and the transverse mesocolon, and then wrapped in omentum to lessen the risk of future diathermy damage to the gastrointestinal tract. Direct rigid ureteroscopy in the course of this procedure revealed several tiny upper ureteric tumours which were treated by combined suction and diathermy (Bunce *et al.*, 1991). Histology of these tumours showed pT1G2 transitional cell carcinoma. We have performed multiple ureterorenoscopy procedures, suction diathermy treatment and intrapelvic instillations of Mitomycin C for recurrent and residual upper tract tumours via the ureterostomy with easy access.

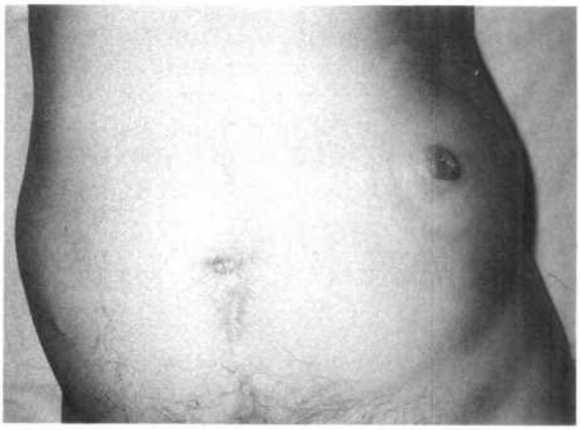
Fig. 2 Patient's anterior abdomen showing the position of the left upper quadrant end ureterostomy as urinary diversion.

Comment

Various permanent urinary diversion techniques are described in the literature, ranging from ureterosigmoidostomy, permanent nephrostomy, ileal or colonic conduit, cutaneous ureterostomy, ring ureterostomy or ureterostomy-en-Y. Ureterostomy was first suggested in 1856 by Gignon, but it was not until 43 years later that LeDentu performed the first deliberate cutaneous ureterostomy.

Our patient had a dilated but functioning left kidney associated with multiple tumours within its pelvicaliceal system. If these could be destroyed and recurrent tumours controlled by endoscopic means, preservation of the solitary kidney and its function might be achieved. If renal access were provided by some form of urinary diversion, one might avoid or postpone permanent dialysis or renal transplantation. The "ideal" diversion would be one which could be easily performed, could offer direct access to the renal pelvis with rigid endoscopes and could provide good urine drainage. Possible contenders included ureteroileal or uretero-colonic conduit diversion, permanent nephrostomy, pyelocutaneous ileal or colonic conduit, or autotransplantation of the kidney to the iliac fossa with anterior pyelostomy. Lloyd *et al.* (1962) described the technique of high lateral cutaneous ureterostomy (midway between the twelfth rib and iliac crest over the anterior axillary line) and had good results with over 20 patients. Young and Aleida (1966) had satisfactory results with flank ureterostomy for unilateral diversion in 11 patients. We favoured anterior upper quadrant ureterostomy in the presence of multiple intrarenal tumours and a dilated ureter for its advantage of simplicity, direct easy access to the renal pelvis by rigid instruments and avoidance of the risk of track seedings associated with nephrostomy. There is also less risk of stomal stricture in the presence of the dilated ureter, shorter ureteric length with reduced risk of ischaemia. Having to wear braces instead of a belt for his trousers is probably a small price to pay.

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Endoscopic Removal of Non-deflating Foley Balloon Catheter

K. SUBRAHMANYAM, P. SRIDAR, K. VENUGOPAL and B. SURYAPRAKASH, *Department of Urology, Nizam's Institute of Medical Sciences, Hyderabad, India*

Removal of a Foley catheter can sometimes be difficult because of a blocked balloon channel. Techniques used to overcome this problem include injection of ether into the balloon and transrectal or transabdominal puncture of the balloon. We describe a new endoscopic technique for puncturing the balloon.

The catheter is cut about 2.5 cm beyond the external urethral meatus and a long thick silk stay suture is inserted into the end of the catheter. Under local analgesia the catheter is pushed into the bladder followed by a 19F cystoscope. Once the entire catheter is in the bladder a ureteric catheter stylet is passed through the cystoscope and the balloon is punctured. The catheter can then be removed by applying traction to the silk stay suture. This technique has been used successfully in 2 patients.

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Simple Technique for Everting a Spout Ileostomy

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A simple technique is described to evert small bowel when fashioning a spout ileostomy as used for urinary diversion.

When forming an ileostomy it is important that a spout is created in order to protect the skin from irritation. Everting the small bowel to form the spout can be awkward and grasping the mucosa with instruments such as Babcock forceps may result in unnecessary tearing and bleeding.

We recommend the use of a conventional adult Langenbeck retractor. If the small bowel is rolled over the upturned blade of a Langenbeck retractor (Fig.) eversion can be achieved with minimal trauma to the small bowel. Traction may be applied to the small bowel with stay sutures. The blade of

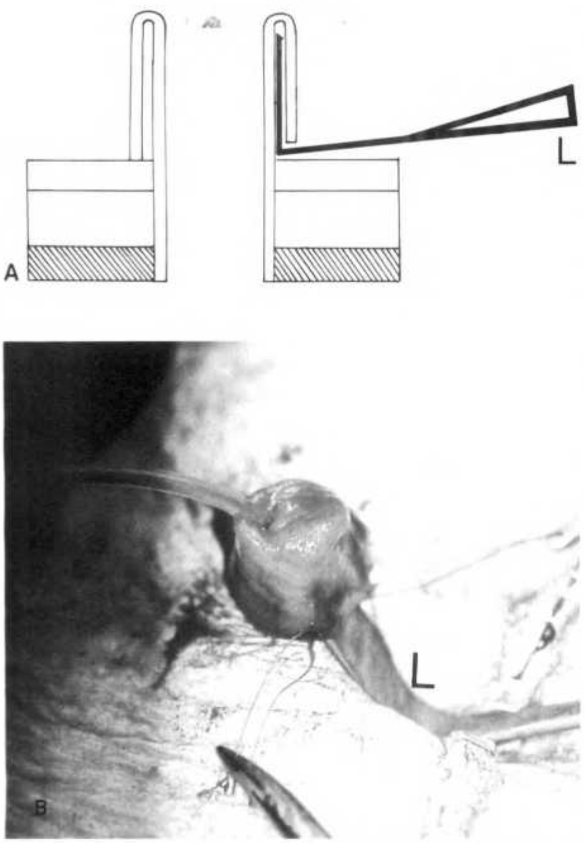

Fig. Diagrammatic (A) and clinical (B) illustration of ileum everted over a Langenbeck retractor (L).

the retractor is 4 cm long and hence the spout will be the same length. This results in a stoma which is easy to manage and affords good skin protection. This simple technique not only assures the correct length of ileostomy spout but also reduces trauma during eversion and saves time.

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Percutaneous Dilatation of Difficult Nephrostomy Tracts

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Many techniques have been used to establish a percutaneous nephrostomy tract suitable for nephroscopy and nephroscopic surgery. Dilatation of the tract is often difficult in the presence of a tough thoraco-lumbar fascia or extensive perirenal fibrosis following previous renal surgery. A method is described which facilitates dilatation in situations where the procedure is difficult because of perirenal fibrosis.

Technique

Placement of a guide wire in the renal pelvis usually proceeds without difficulty, even in the presence of extensive perirenal fibrosis. However, dilatation from this point may be impossible using semi-rigid dilators (such as the Amplatz renal dilators) (Coleman, 1986). The dilator passes readily to the level of fibrosis and will pass no further, as the relatively flexible small dilator will buckle when it encounters the fibrous tissue (Fig. 1). This buckling effect may be overcome by dilating the tract down to the level of the fibrosis without attempting to pass the dilator through the area of high resistance, and then passing a smaller dilator (Fig. 2). The large dilator prevents buckling of the small dilator in the soft tissues overlying the fibrosis. This allows penetration of this tough tissue and, having initially being breached, further dilatation of the fibrotic area can usually be achieved with little difficulty.

Comment

Many methods are available for dilatation (Mazzeo *et al.*, 1982; Ware, 1982) but we feel this technique has certain advantages in situations where dense fibrosis is encountered in the perirenal tissue.

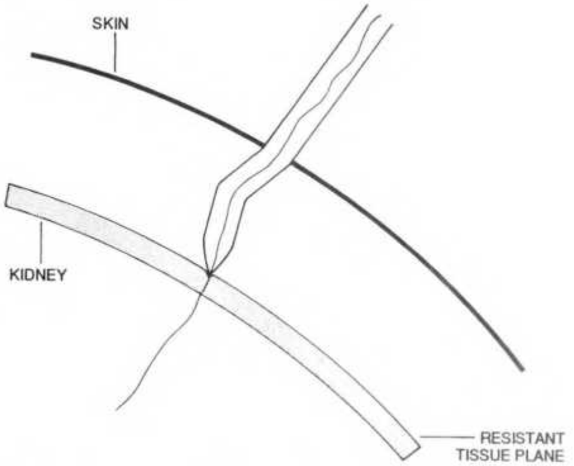

Fig. 1 Thin dilator bends when tough tissue is encountered, making further progress impossible.

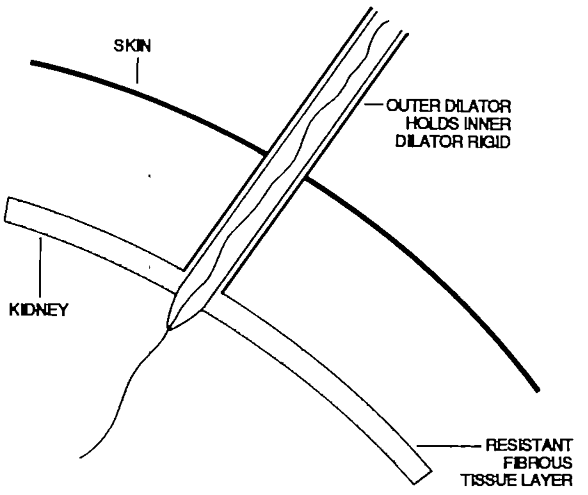
SKIN
OUTER DILATOR HOLDS INNER DILATOR RIGID
KIDNEY
RESISTANT FIBROUS TISSUE LAYER

Fig. 2 Outer dilator holds inner dilator straight. Force is then transmitted to the tip of the thin dilator, assisting in penetration of the tissue planes

Proximity to the kidney makes vigorous and uncontrolled methods of dividing the tough tissue more than usually hazardous. Fascial lumbotomes are an excellent means of dividing tough fascia but they are not intended for use in the perinephric area, where there is a significant risk of damage to the kidney.

Telescoping metal dilators are often used for percutaneous tract dilatation and they also cope well with dense perinephric fibrosis. One of their disadvantages is the rigidity of the tip dilator, which is associated with a higher incidence of damage to the renal pelvis, and this normal risk is further increased by the force necessary to achieve dilatation. Also, with metal dilators there is no tamponading effect of a permanent outer sheath during the pyelolithotomy and/or pyelolithotripsy. These procedures in such patients often involve multiple withdrawals and insertions of the nephroscope, as they tend to be complex cases and a one-step manoeuvre is not possible.

When a thin dilator (6.5 or 8 F) encounters marked resistance from scar tissue, increased force usually results in bowing of the shaft of the dilator. By dilating down to the level of resistance rather than attempting to penetrate the scar tissue it is possible to introduce a large dilator into the more superficial part of the tract. This large bore dilator then holds the thin dilator straight while it penetrates the resistant tissue planes. Thus one achieves the rigidity necessary to perform dilatation through dense perirenal fibrosis, while maintaining the advantages of a system which uses a flexible dilator which minimises damage to the renal pelvis. The external sheath also provides tamponade and tissue protection during what is usually a long and difficult procedure.

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Pre-vesical Ureteric Calculi: Modified Prone Position for Extracorporeal Shock Wave Lithotripsy using the Siemens Lithostar

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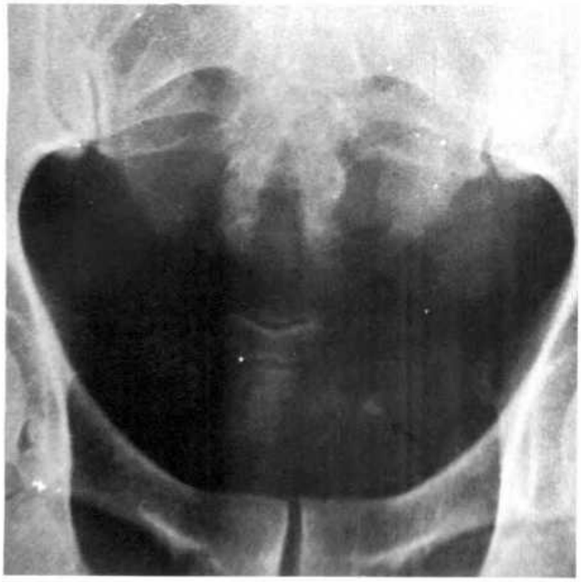
Extracorporeal shock wave lithotripsy (ESWL) is an accepted treatment for renal and upper ureteric calculi and is being increasingly used to treat lower ureteric calculi, with ureteroscopy now limited to difficult or failed cases (Dretler, 1990). The main problem in treating pre-vesical calculi with ESWL lies in finding a suitable shock wave path, since the calculi are surrounded by bone and are usually treated through the greater sciatic foramen with the patient lying either supine (Holden and Rao, 1989) or in one of the other modified positions (Becht *et al.*, 1988). When using the blast path in the supine position with a Siemens Lithostar we found it difficult to separate bone from the pathway of shock waves, resulting in pain and poor fragmentation. We considered using the pelvic brim as the entry pathway in the prone position, but calculi tended to slip behind the pubic symphysis, making fluoroscopic focusing and treatment difficult. We now use the modified prone position as described below.



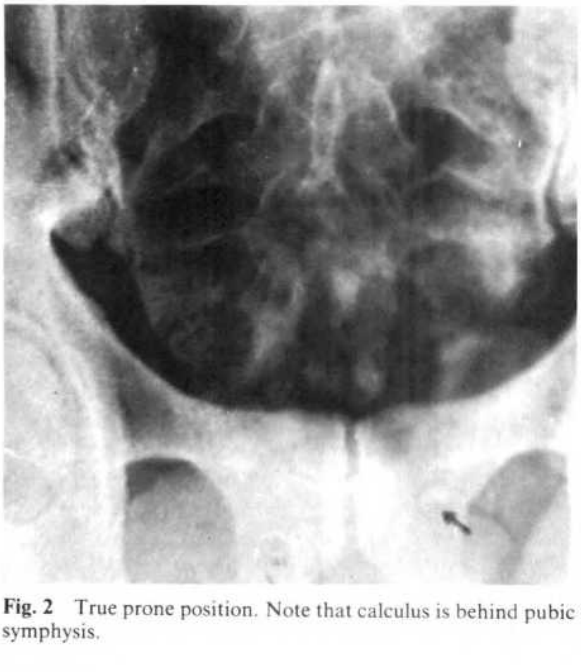


Fig. 2 True prone position. Note that calculus is behind pubic symphysis.

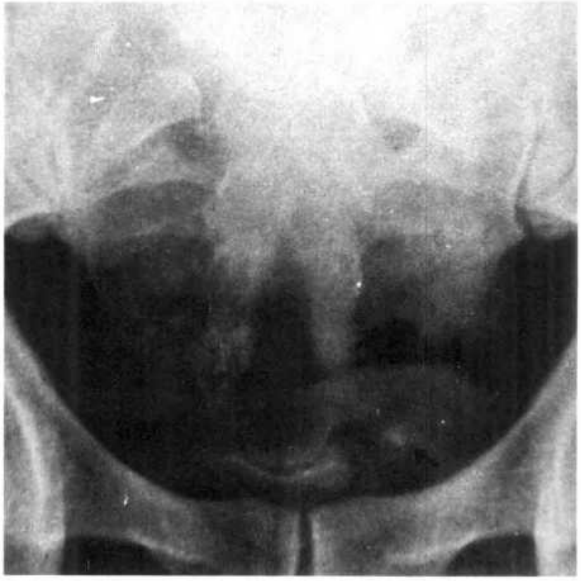


Fig. 3 Modified prone position. Pelvic brim rotation has brought the calculus back into view.

Technique

The patient lies prone on the Lithostar table with a full bladder. A pillow is placed beneath the thighs to raise the knees by 15 to 20 cm and so hyperextend the hip joints. This increases the lumbar lordosis and opens up the face of the pelvic brim to the shock wave head (Figs 1–3), bringing the calculus back into the view from behind the pubic symphysis. The calculus can then be easily focused and treated.

Comment

The position described assists biplanar localisation and the fragmentation of pre-vesical calculi with higher shock wave energy and with little need of analgesics. If the patient experiences pain, this can be alleviated by the partial interposition of foam sheet between the shock wave head and the superior pubic ramus. The full bladder improves the fluoroscopic image and also provides a good path for the transmission of shock waves. Careful selection of patients is necessary because not all patients, particularly those with arthritis of the spine, can lie in the modified position for the duration of treatment.

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Notices

British Association of Urological Surgeons
President: J. C. Smith, MS, FRCS

Annual Meeting: Harrogate, 22–25 June 1993

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1992. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 8th January 1993.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

British Association of Urological Surgeons

Autumn Meeting: Taliesin Theatre, University College, Swansea. 9 and 10 October 1992

Friday, 9 October: Urogynaecology.

Saturday, 10 October: Programme of Local Clinical and Scientific Papers.

Further information from: BAUS Secretariat, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

William Cook Travelling Fellowship

In 1990, William Cook Europe Limited generously offered an annual sum of £3000 to finance a minimum of three travelling fellowships each year. Candidates must be members of the British Association of Urological Surgeons. Applications should be made to the Honorary Secretary of BAUS by 1 February, giving the following information: the name of the centre to be visited, the reason for the visit and an estimate of the cost of travel and accommodation. Prior agreement to the visit must be obtained from the surgeon/hospital in question.

Applications will be considered by a BAUS Committee. Successful applicants will be required to submit a report on the experience gained in the centre visited.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and 3 copies must be submitted by 1 October 1992 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Kellerhals & Partner, P.O. Box, CH-3000 Bern 7, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

Institute of Urology and Nephrology (University College London) in association with St Peter's Hospital

Preliminary Academic Programme 1992/1993

15–16 October 1992
Spinal Injury Management for Urologists (BAUS/SCOPE meeting

29–30 October 1992
Urology for General Practitioners

4 November 1992
Platelets and Endothelium in Renal Disease

11 December 1992
Urolithorama

11–22 January 1993
Short Courses in Urology and Nephrology (including Urological Cancers; Upper Tract Obstruction; Stone Disease; Prostatic Disease; Trauma)

11 February 1993
Uro-radiology

February 1993
Advances in Minimally Invasive Surgery

15–18 March 1993
Uro-andrology

19–20 March 1993
International Symposium of Operative Andrology

March 1993
New Techniques in Prostatic Outflow Obstruction

April 1993
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19 April–7 May 1993
Short Courses in Urology and Nephrology (including Female Urology; Reconstructive Surgery; Paediatric Urology; The Elderly; Tropical Diseases; Urology of the Future)

For further information please contact: The Course Secretary, Institute of Urology and Nephrology, 48 Riding House Street, London W1P 7PN. Tel: 071 380 9381/9372.

N.B. Please note that the Surgitek Prize, which was announced in the July and August issues, has been discontinued.

Erratum

re **Prevention of vesicoureteric reflux by endoscopic injection.** P. Frey and R. H. Whitaker.
Br. J. Urol. (1992), **69**, 1–6.

Part of the first sentence in the Results section on page 3 is incorrect. It should read: "In the series by Puri (1991) of 123 patients treated between 1984 and 1988 . . . ". The full reference is "Puri, P. (1991). Endoscopic correction of primary vesicoureteric reflux by subureteric Teflon injection (STING): follow-up study in 123 patients. *Ped. Surg. Int.*, **6**, 269–272." The authors apologise for this error.

British Journal of Urology (1992), **70**, 460–461

Diary

1992

October 1–2	Continuing Medical Education and Training in Europe: the Future. London. Contact: Dr M. W. N. Nicholls, Conference Office, c/o Fellowship of Postgraduate Medicine, 6 St Andrew's Place, London NW1 4LB. Tel: (44) (0)71 935 5556. Fax: (44) (0)71 224 3219.
October 1–3	Annual Meeting of the Swiss Society of Urology. Leysin, Switzerland. Contact: Prof. Dr P. Graber, Clinique de Chirurgie Urologique, Hôpital cantonal, CH-1211 Genève 4, or Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich.
October 1–3	Fourth World Congress of VideoUrology. Monte Carlo, Monaco. Contact: Convergences—VideoUrology '92, 120 Avenue Gambetta, 75020 Paris, France. Telex: 216 911 F. Fax: (33-1) 40 31 01 65.
October 3	Meeting of the Belgian Association of Urology. Bruges, Belgium. "Early diagnosis and treatment of localized carcinoma of the prostate". Contact: Dr J. Ampe, Department of Urology, A.Z. St Jan, Ruddershove 10, 8000 Brugge, Belgium.
October 6–9	27th Annual Meeting of Egyptian Urological Association. Alexandria, Egypt. Contact: Dr Mamdouh Koraitim, Department of Urology, Faculty of Medicine, Alexandria University, Alexandria, Egypt.
October 7–11	1992 Duke Urologic Assembly. "Contemporary Issues in Urology". Pinehurst, North Carolina. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
October 8–11	International Congress: History, Knowledge & Quality of Life In Urology, Fiuggi, Italy. Contact: Prof. P. Marandola, Università di Pavia, Policlinico S. Matteo, Istituto di Clinica Chirugica, P. le Golgi 2,27100 Pavia, Italy. Tel: 39 382 423265.
October 9–10	BAUS Autumn Meeting, Swansea. Contact BAUS Office.
October 15–16	European School of Oncology. 10th Anniversary Events. Milan, Italy. Contact: European School of Oncology, Via Venezian 18, 20133 Milan, Italy. Tel: (+39 2) 70635923-2364283. Fax: (+39 2) 2664662.
November 1–4	Third International Workshop on Carcinoma *in situ* and Cancer of the Testis. Copenhagen, Denmark. Contact: Workshop Secretariat, c/o Professor N. E. Skakkebaek, University Department of Growth and Reproduction, Section 5064, Rigshospitalet, 9 Blegdamsvej, DK-2100, Copenhagen, Denmark.
November 8–10	Fourth International Conference of the Society for Minimally Invasive Therapy. Dublin, Ireland. Contact: Professor J. Fitzpatrick, 47 Eccles Street, Dublin 2, Ireland. Tel: +353-1-308530. Fax: +353-1-300345.
November 27–28	International Postgraduate Course on Reconstructive Surgery of the Lower Urinary Tract in Children. Amsterdam, The Netherlands. Contact: Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands: Tel: +31 20-566 4801. Fax: +31 20-696 3228.

December 4–5	Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.

1993

January 26–29	Ninth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev, Denmark. Contact: Dr F. Rasmussen, Department of Urology, Herlev Hospital, DK-2730 Herlev, Denmark.
March 14–15	State-of-the-Art Genitourinary Ultrasound Course. Honolulu, Hawaii. Contact: American Institute of Ultrasound in Medicine, Convention Department, 11200 Rockville Pike, Suite 205, Rockville, Maryland 20852, USA. Tel: (301) 881-2486. Fax: (301) 881-7303
March 19–20	Second European Congress on Ambulatory Surgery. Brussels, Belgium. Contact: Dr C. De Lathouwer, Brussels One Day Clinic, Avenue du Duc Jean 71–73, B-1080 Brussels, Belgium. Tel: +322/424.1212. Fax: +322/425.7076.
March 27	First International Symposium on Bladder Cancer. "BCG immunotherapy in superficial bladder cancer. The 1993 state of the art". Padova, Italy. Contact: Professor F. Pagano, Department of Urology, University of Padova, Via Guistiniani 2, 35128 Padova, Italy. Tel: 049-8212720. Fax: 049:8212721.
April 19–22	2nd Interamerican Meeting on Pediatric Urology. Viña Del Mar, Chile. Contract: Dr Ricardo Gonzalez, 420 Delaware Street, S.E. Box 45, University of Minnesota Hospital, Minneapolis, Minnesota 55455, USA. Tel: 612 625-9117. Fax: 612 626-2458 *or* Dr Ricardo Zubieta, Esmeralda 678, 3 er Piso, Of. 303, Casilla 639, Santiago, Chile. Tel: 56-2-331. Fax: 56-2-391 085.
May 16–20	American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
June 4–5	Fifth International Meeting of Andrology. "Corporal Veno-occlusive Dysfunction: Diagnosis and Treatment". Rome, Italy. Contact: Dr Diego Pozza, Centro di Andrologia e di Chirurgia Andrologica, via Flaminia Nuova 280, 00191 Rome, Italy. Tel. and Fax: +39.6-3270741.
June 20–24	Canadian Urological Association Annual Meeting, Bonaventure Hotel, Montreal, Quebec. Contact: To be announced.
September 26–30	International Symposium on Sex Hormones and Anti-hormones in Endocrine-dependent Pathology: Basic and Clinical Aspects. Milan, Italy. Contact: M. Motta or M. Serio, Department of Endocrinology, University of Milan, 9 Via Balzaretti, 20133 Milan, Italy. Tel. 02-20406576. Fax: 02-29404927.
November 4–6	Second International Congress of the Dutch Urological Association. "New Insights into the Aetiology, Diagnosis and Management of BPH". Amsterdam, The Netherlands. Contact: IMEDEX, P.O. Box 3283, 5203 DG 's-Hertogenbosch, The Netherlands. Tel: +3173429285. Fax: +3173414766.

1994

May 15–19	American Urological Association, Moscone Centre, San Francisco, California.

British Journal of Urology (1992), 70, 462–463

Book Reviews

Diagnosing Male Infertility. New Possibilities and Limits. (Progress in Reproductive Biology and Medicine). Volume 15. Edited by G. M. Golpi and D. Pozza. Pp. x+250. Basel, Munchen, Paris, London, New York, New Delhi, Bangkok, Singapore, Tokyo, Sydney: Karger. 1992. Price: £107.00.

This book will be of interest to specialists in andrology and infertility. There are 34 short chapters giving updates on various aspects of the investigation and treatment of male infertility Some of the contributions are in the form of preliminary investigations or are based on small personal experiences of unproven technology. There is much in this book for the enthusiast but it is not a book for those who are starting to specialise in andrology, or infertility.

Bailey & Love's Short Practice of Surgery. 21st edition. Revised by C. V. Mann and R. C. G. Russell. Pp. xvi+1519. London, New York, Tokyo, Melbourne, Madras: Chapman & Hall Medical. 1992. Price: £49.00.

In this, the 21st edition, the new editors aim, as did all previous ones, at giving trainee surgeons, students and others the essential framework of the modern practice of surgery. While this includes the latest methods of investigation and treatment, it recognises that their cost often precludes their use in many parts of the world; accordingly it remains true to the ideals of the original editors in stressing the basic techniques that can be used in any part of the world.

A new chapter has been added on accident and emergency surgery. The others have all been rewritten and furnished with many new figures and illustrations, but retaining many of the old favourites. Although the section on urological surgery may appear superficial to trainees in that specialty it is perfectly adequate for those to whom the book is directed, including those for whom urology is a brief part of a rotation.

The editors and contributors are congratulated on maintaining the excellent standards of the previous editions of this deservedly popular textbook, and the publishers for producing such a handsome volume at a price of £49.00.

This book is thoroughly recommended to undergraduates, to postgraduates studying for the basic Fellowship examination, to nurses who remain in clinical contact with patients, and to general practitioners, especially those involved in immediate medical care.

Testicular Cancer: Investigation and Management. Edited by A. Horwich. Pp. xv+373. London, New York, Tokyo, Melbourne, Madras: Chapman & Hall Medical. 1991. Price: £65.00.

For several years now, testicular cancer has represented the paradigm for the successful management of solid tumours. The availability of sensitive and specific tumour markers and radiological means of monitoring tumour status, together with developments in treatment, have allowed continuous refinement of management policies, so that attention has increasingly turned to means of achieving the same level of success with decreased treatment morbidity in both the short and long term. Success, however, has not diminished controversy, and this volume by 29 authors from 9 countries brings together the background to these developments and describes in detail the areas of continuing debate. The emphasis is very much on investigation and management, and this is not the place to seek a detailed account of pathology (one page) or aetiology (one page). On the other hand, the transatlantic differences in approach to the management of stage 1 non-seminoma is informatively ventilated with an excellent review of the rationale and Medical Research Council experience of surveillance as a policy, followed by chapters on the rationale and surgical techniques for lymphadenectomy and the nerve-sparing techniques as practised in Indiana. Few will be surprised by the conclusions reached by each author, but the arguments on both sides are lucidly expressed. The management of metastatic seminoma and non-seminoma is comprehensively reviewed with particularly useful chapters reviewing the evolution of effective chemotherapy and the toxicity, both physical and psychosocial. In this context the risks of pulmonary fibrosis and possibly increased myelosuppression related to the use of bleomycin in the management of "good-prognosis" non-seminoma are well reviewed and put into context. The role of surgery for residual masses following chemotherapy has been the subject of considerable debate, and the large Royal Marsden Hospital experience of both abdominal surgery and thoracotomy is an important contribution. The reminder to prepare the patient early for the possibility that surgery may be required for any residual mass and that the need for such surgery does not represent treatment failure should be borne in mind by all those involved.

Overall, this book is a comprehensive and well referenced review of current practice and outstanding problems in the treatment of testicular tumours. There are some inevitable duplications, and some proof-reading errors could cause confusion at first sight (the mortality rate in patients with metastatic non-seminoma and none of the adverse features listed on page 10 is surely 7% rather than the 70% quoted). It does not set out to be a comprehensive textbook, but all those involved in managing patients with testicular tumours, or answering examination questions about their management, will find the important issues thoroughly debated.

Cellular and Molecular Biology of the Kidney. (Contributions to Nephrology Series, Volume 95). Edited by H. Koide, H. Endou and K. Kurokawa. Pp. iv+288. Basel, Munich, Paris, London, New York, New Delhi, Bangkok, Singapore, Tokyo, Sydney: Karger. 1991. Price: £107.40.

Contributions to Nephrology continues its series of providing up-to-date reviews and discussions of topics in basic research which are relevant to those working in renal medicine or surgery. This volume is the proceedings of an International Symposium on Cell Biology on Nephron Heterogeneity held in Japan in 1990. This is a text for molecular biologists and those interested in the mechanisms of cell regulation within the kidney, but even a passing glance is of interest to most nephrologists and urologists who are interested in keeping abreast of the cutting edge of our discipline. There are a number of papers on the effects of ureteric obstruction and its effect on glomerular filtration but otherwise most of the papers on sodium, potassium and acid base balance, signal transduction and cell volume regulation are at a more basic level. The highly specialised papers on the function of the mesangium and its relationship to glomerular function are fascinating but of little clinical application yet. The book is well produced with beautiful diagrams, electron micrographs and the clearest gels I have ever seen reproduced. There is a heavy preponderance of Japanese authors, which illustrates the major contribution they are now making in this field.

Comparative Spermatology 20 Years After. (Serono Symposia Publications from Raven Press, Volume 75). Edited by B. Baccetti. Pp. xxxvi+1112. New York: Raven Press. 1992. Price: US$219.00.

This book is a series of reports on various aspects of biology and molecular biology of sperm from man and other species. Many of the chapters are laboratory or research reports rather than comprehensive reviews and the book is a cross between a journal and a text. There is a wealth of material within it and it will be a source book for sperm scientists, but the practising clinician may safely leave it in the library.

The Kidney. Physiology and Pathophysiology. Second edition. (3-volume set). Edited by D. W. Seldin and G. Giebisch. Pp. 3952. New York: Raven Press. 1991. Price: US$531.50.

This mammoth 3-volume work describes the physiological and molecular principles underlying the exchanges of water and electrolytes and the role of the kidney in responding to normal and abnormal disturbances.

After a fascinating history of renal physiology to 1950 the book is divided into 4 sections.

Section 1 describes the general principles of water and electrolyte regulation within the compartments of the body. Compartmental exchanges are explored and the basic principles underlying solute and solute transport are described. The molecular biology of transport is considered with emphasis on renal development, epithelial cell structure and traffic, transport proteins and cell signalling.

Section 2 describes the organisation of the kidney in 3 subsections: (1) the structure and development of the kidney, (2) functional organisation (renal circulation, haemodynamics, nephron segments and nephron heterogeneity) and (3) the kidney as an endocrine organ controlling blood pressure, bone and bone marrow.

Section 3 deals with normal and abnormal water and electrolyte exchange.

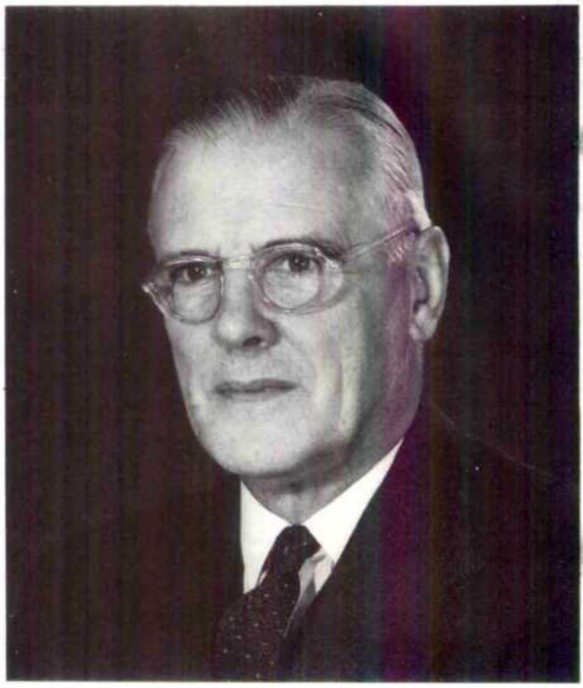
Section 4 considers the mechanisms of extrinsic and intrinsic renal failure and the actions of various pharmacological agents.

At a price of US$531.50 for the 3-volume set this is not a book that every urologist would wish to have in his own personal library. However, as a reference text and as a source of the underlying principles of normal and abnormal physiology of the kidney it should be in the library of every department.

British Journal of Urology (1992), **70**, 464

Obituary

Mr Victor Dix, MRCP, FRCS



Victor Dix died on 29 June 1992, aged 93. He had been one of the founders of BAUS and was its President in 1962. Although he remained a general surgeon, he created one of the first dedicated urological departments in Britain at the London Hospital and laid the plans which made it possible for his successors to have a "pure" urological firm within a few years of his retirement.

He entered the London Hospital Medical College in October 1921, qualified with the conjoint in 1923, the Cambridge MB, ChB in 1925, and took the MRCP and FRCS in 1926, was house surgeon to James Sherren, and First Assistant to Russell Howard and George Neligan, who kindled his interest in urology. Dix was appointed to the staff of the London Hospital as Assistant Surgeon in November 1930, joining Frank Kidd (who had founded this Journal the previous year) in his private practice.

Dix had been sent to Berlin to learn the new method of intravenous pyelography, then being developed by von Lichtenberg. The new technique made it possible to diagnose hydronephrosis at an earlier stage, and this in turn led Dix to improve von Lichtenberg's method of pyeloplasty. In the diagnosis of ureteric stones he developed a simple but certain method of stereoradiography, while his operation for ureterolithotomy was unrivalled for speed and simplicity. The end of the war found Dix in Malaya, where he received an invitation to become Professor of Surgery at the London.

Dix was a very rapid and sure operator but difficult to assist because he habitually wore a headlamp, which became exceedingly hot—a constant hazard to his assistants. He wrote on hydronephrosis and torsion of the appendix testis, but the work of which he was most proud was the technique of open cystodiathermy and radon seed technique for carcinoma of the bladder. In the last 5 years before his retirement he put immense effort into editing the vast Springer Encyclopaedia of Urology.

When Neligan retired in 1950, Dix and his younger colleague Gerald Tresidder set up a new out-patient urological department at the London Hospital, with its own X-ray unit. Here intravenous and retrograde urograms were done in large numbers and every variety of endoscopic operation was performed.

It was the era of retrograde urography, and the Howard and Stamey tests for renal hypertension and measurement of renal blood flow with radioactive rubidium.

Victor Dix was President of the Section of Urology of the Royal Society of Medicine in 1954; he served on the Court of Examiners of the Royal College of Surgeons. He was a member of the American Association of Genitourinary Surgeons. He had a striking appearance—tall and handsome; he was always polite and courteous. His hobbies included tennis, mountaineering and photography, but his passion was for opera, at which those who knew him best were sometimes surprised to see this unrufflable olympian moved to tears. Troubled by a knee injured in a mountaineering accident, and plagued from time to time by recurrent bouts of infection with *Psittacosis bedsonii* (ironically Bedson was one of his close friends and colleagues), he remained fit until quite recently, and died at the age of 93, leaving a widow, two daughters and a son.

J.P.B.

British Journal of UROLOGY

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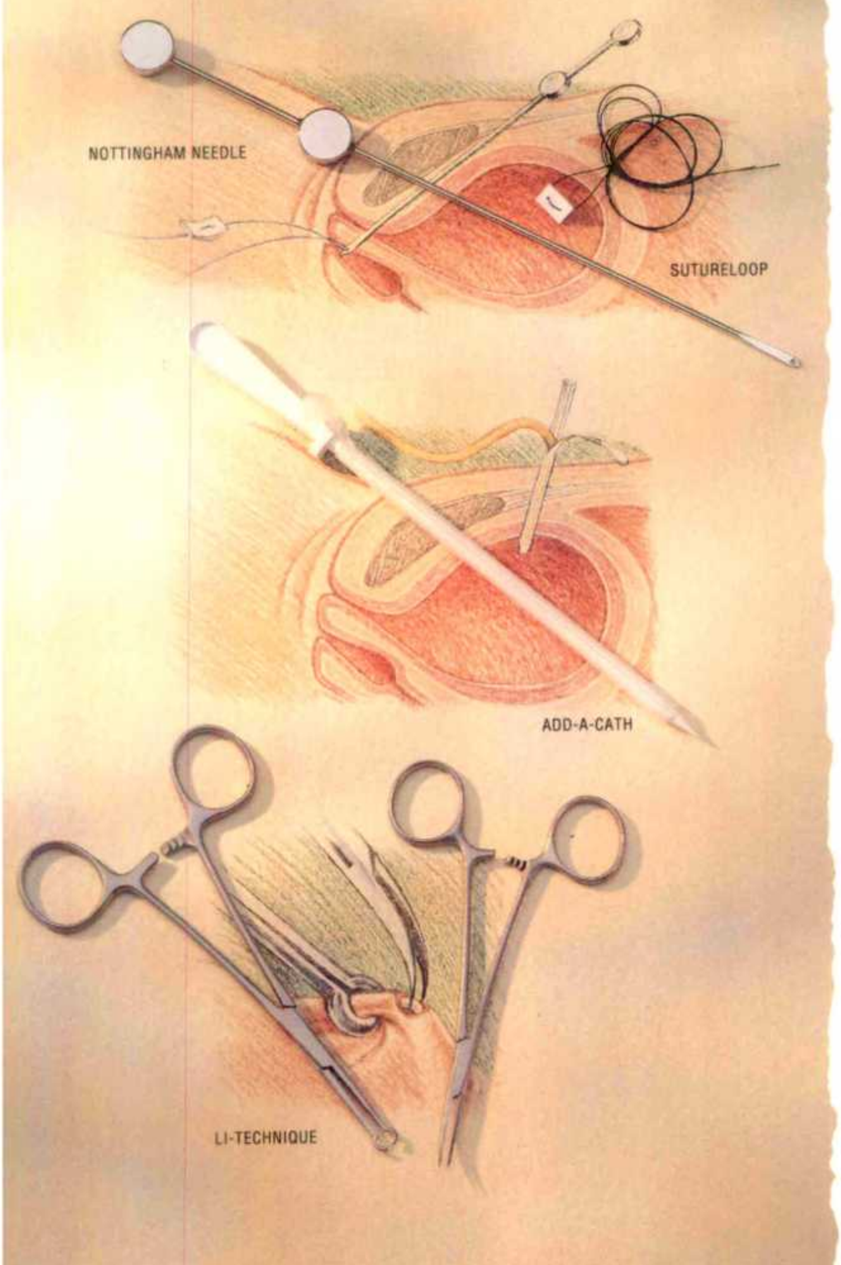

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References to books should be as follows

Wright, F. S. and Howards, S. S. (1981) Obstructive injury. In *The Kidney*, ed. Bremner, B. M and Rector, F. C. Second edition Volume II. Chapter 38, pp 2009–2044 Philadelphia · Saunders.

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REVIEW

Immunotherapy and Chemotherapy for Carcinoma of the Kidney

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The results of treatment for renal cell carcinoma of the kidney have changed little over the last 20 years, with one-third of patients alive 5 years after diagnosis (Cancer Registry Figures). Surgical removal of the primary tumour prior to the development of metastatic disease remains the only established curative treatment and it is difficult to see the surgical results being improved unless earlier diagnosis can be carried out. The purpose of this review is to discuss some of the other treatments now being used for the two-thirds of patients who present with or later develop metastatic disease. The question that most urologists will ask is whether it is better to refer their patients with advanced disease to a specialist oncology centre, where they may be given various toxic drugs, or advise them to go on a long holiday while they are still fit enough! At present it would appear that most British urologists prefer the latter option, since only a minority of patients with metastatic disease receive specific anti-cancer therapy. This review addresses this question and makes some suggestions on when specialist referral is appropriate.

Two points need to be considered when assessing the results of systemic treatment for patients with advanced disease. First is the often indolent natural history in a minority of patients, with little evidence of disease progression over many years. Thus unlike, for example, metastatic lung cancer, there is a small (4–11%) but significant number of 5-year survivors (Van der Werf-Messing and Schroeder, 1982). The second point is the well recognised phenomenon of spontaneous regression of metastases. The reported incidence of this from retrospective studies varies from less than 1% to more than 20% (Van der Werf-Messing *et al.*, 1978). Most of this variation is due to different criteria in assessing "regression" and differences in patient characteristics. Regression is most likely to occur in male patients with pulmonary metastases. A prospective study in 73 patients revealed an incidence of significant regression in 7% (Oliver *et al.*, 1989). What is clear is that nephrectomy in the presence of metastatic disease does not increase the incidence of regression, since only 4 of 474 patients in 9 series experienced regression (Montie *et al.*, 1977).

Hormone Therapy

Systemic treatment of carcinoma of the kidney can be divided into 3 categories: hormone treatment, cytotoxic chemotherapy and immunotherapy. Hormone therapy developed from experimental work in animals which showed that renal tumours could be modulated by hormonal influences. More recent work has shown the presence of progesterone, oestrogen and androgen receptors on the cells of some human cancers, but unlike breast cancer, for example, this does not appear to correlate with response to hormone therapy. Initial reports (Bloom, 1971) suggested a response rate of approximately 20% to medroxyprogesterone acetate (Provera) but more recent studies using more stringent criteria in assessing response have shown response rates of less than 5% and this "response" may merely be a manifestation of spontaneous regression (Hrushesky and Murphy, 1977). Other hormonal agents, including androgens and anti-oestrogens such as tamoxifen, have also shown response rates of less than 10%. Similarly, the use of progesterones in an adjuvant context after nephrectomy did not reduce the rate of subsequent relapse in a randomised study by Pizzocaro *et al.* (1987). Despite these unimpressive figures the use of hormones remains

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popular and it is still the most commonly used therapy in Britain. The reasons for this continued popularity are probably its ease of administration and lack of major toxicity; it also enables the clinician to offer some "treatment" to the patient. Some hormones, such as the progesterones, have the added advantage of improving appetite and general well-being and, along with corticosteroids, this can be sufficient justification for their use.

Chemotherapy

Cytotoxic chemotherapy is almost as ineffective as hormone therapy and has the disadvantage of greater toxicity. Of established agents, vinblastine appears to have the highest response rate, but the initial report of a 30% response rate has since been diluted to approximately 15% (Hrushesky and Murphy, 1977). Response rate in this context merely implies a temporary, greater than 50% reduction in size of a measurable tumour; the duration of response is usually short, with no evidence of a significant improvement in survival. While the toxicity of vinblastine is modest compared with that of some cytotoxic agents, side effects include nausea, vomiting, myelosuppression, alopecia and neurotoxicity. In an attempt to improve these results, investigators have combined other cytotoxic agents with vinblastine and higher response rates have occasionally been observed (Bell *et al.*, 1984), albeit with greater toxicity. Of the newer agents, flurodeoxyuridine appears the most encouraging and produced a response rate of 33% when given by continuous infusion (Hrushesky *et al.*, 1987). The author's opinion is that the routine use of cytotoxic chemotherapy cannot be recommended, although well motivated patients can be considered for Phase I/II studies of new agents.

Immunotherapy

The final category of treatment to be considered is immunotherapy. This has stimulated tremendous interest not only in the medical literature but also the non-medical media. The concept of a naturally occurring substance being used to stimulate the immune system and thus destroy the cancer has obvious popular appeal and both interferon and interleukin 2 (IL-2) were widely publicised as "the breakthrough" in the search for a cure for cancer. Sadly, despite massive research effort over the last 2 decades, immunotherapy has at present only a limited place in the treatment of cancer. There does, however, appear to be a place for immunotherapy with carcinoma of the kidney, where not only have response rates been greater than those reported for most other solid tumours but also, as already discussed, there is a lack of effective alternative treatments. A range of treatments has been tried and some are listed in the Table. The two that have stimulated most interest are the cytokines interferon and IL-2.

Table Immunotherapy of Renal Carcinoma

Agent	*Actions*
Interferons α, β, γ	Antiproliferative and activates NK cells, T lymphocytes and macrophages
Interleukin-2	Stimulates growth of T lymphocytes
Lymphokine activated killer cells	Direct cytotoxicity against tumour cells
Tumour infiltrating lymphocytes	Direct cytotoxicity against tumour cells
Coumarin and cimetidine	Non-specific immune stimulation?

There are 3 types of interferon: α (leucocyte derived), β (fibroblast derived) and γ. Initial studies used impure preparations of interferon which were tedious and expensive to produce. The advent of recombinant DNA technology has allowed large amounts of pure interferon to be produced at a relatively modest cost. Most experience to date is with α interferon, which has direct cytotoxic effects as well as immunomodulatory effects. Many studies have been carried out, usually with small numbers of patients and varying response rates of 6 to 27%. An overview of 1532 patients showed an average response rate of 16% (Horozewicz and Murphy, 1989) Although this is modest, it is higher than might be expected from spontaneous regression. Analysis of patient characteristics has shown good performance status and pulmonary metastases to be the most significant factors for response. Disease-free interval, age and sex were not significant factors. Most studies have used daily intramuscular injections, although the subcutaneous route appears to be equally effective and allows patients to self-administer the drug at home. Ideally, treatment should continue for approximately 3 months before assessing response, since responses may be delayed when compared with cytotoxic chemotherapy. Initial studies attempted to administer the highest possible doses on the basis that this would give the highest response rate, but subsequent studies showed that more was not necessarily better, with response rates of 15% with doses exceeding 10MU, 20% with doses of 5 to 10 MU and 11% with doses less than 5 MU (Muss, 1988). The major side effects are pyrexia, myalgia, nausea, anorexia and CNS toxicity. Essentially the side effects resemble "flu" and can become intolerable over long periods. There are more limited data on β and γ interferon but neither has any definite advantage over α interferon. Patients responding to interferon have a median duration of response of 8 months and survive longer than non-responders (Horoszewicz and Murphy, 1989). What is not clear is whether this increased survival is due to the treatment or due to patient characteristics and biology of the tumours. Unfortunately, no randomised study has been carried out comparing interferon with supportive care only, to determine if overall survival is improved.

IL-2 was first identified in 1976 (Morgan *et al.*, 1976) and termed a T-cell growth factor owing to its ability to stimulate the clonal expansion *in vitro* of T-lymphocytes. Subsequently, IL-2 was found to activate natural killer cells *in vivo* and generates lymphokine activated killer cells (LAK), both of which can destroy tumour cells. Through induction of γ interferon it also enhances the anti-tumour effects of macrophages. Clinical studies of IL-2 were commenced in the 1980s by Rosenberg at the National Cancer Institute. Treatment was termed adoptive immunotherapy and the usual protocol involved administering large doses of IL-2 intravenously followed by leukophoresis to harvest lymphocytes. These were then cultured *in vitro* with IL-2 to generate large numbers of LAK cells which were then reinfused with further IL-2. Other patients received IL-2 alone. Most solid tumours were relatively insensitive but carcinoma of the kidney showed one of the highest response rates, with 35% responding to IL-2 and LAK cells and 21% to IL-2 alone (Rosenberg *et al.*, 1989a and b). Associated with this treatment, however, were not only major financial costs but also major side effects. For a "natural" therapy the latter were impressive, including pyrexia, vomiting, diarrhoea, jaundice, erythrodermia, psychosis, coma, renal insufficiency, myelosuppression, hypotension, cardiac arrythmias, myocardial infarction and respiratory distress. The underlying cause of many of these side effects is a capillary leak syndrome. Because of their cardiorespiratory problems, patients were managed in the Intensive Care Unit and a proportion required ventilation, vasopressor therapy and antiarrythmic drugs (Lee *et al.*, 1989). Not surprisingly in view of these toxicities there has been some debate on the acceptability of such a treatment, particularly in view of its non-curative nature (Moertel, 1986).

Other investigators have either attempted to reproduce Rosenberg's results or tried to reduce the toxicity by using different schedules. A multicentre study in the United States (Fisher *et al.*, 1987), using IL-2 and LAK cells, obtained a response rate of only 16%. It was postulated that the lower response rate was due to the presence of more patients with bulky disease and without prior nephrectomy. A European multicentre study (Negrier *et al.*, 1989) obtained a response rate of 19% for IL-2 alone and 27% for IL-2 and LAK cells. While overall the response rates are similar to those of interferon, the duration is longer and there is also a larger proportion of complete responders (6–10%), some of whom are long-term survivors. More success has been obtained in reducing toxicity. Low doses, although non-toxic, are ineffective, but continuous infusion (giving total doses similar to the bolus treatments given by Rosenberg) has yielded similar efficacy with reduced toxicity and allowed patients to be managed in an ordinary ward (West, 1989). Even more encouraging has been the development of subcutaneous administration, which allows treatment to be carried out at home (Atzopodien *et al.*, 1990). The combination of IL-2 and LAK cells has resulted in slightly higher response rates when compared with IL-2 alone, but the extra costs and laboratory facilities required preclude the use of LAK cells except in the most major (and rich) institutions. Other developments have been the use of IL-2 combined with α interferon (Rosenberg *et al.*, 1989a and b), with no clear benefit, and IL-2 combined with tumour infiltrating lymphocytes (Kradin *et al.*, 1989). The latter involves a protocol similar to that used for the LAK cells but instead of using lymphocytes from the peripheral blood, lymphocytes are extracted from a piece of tumour and then expanded *in vitro*. There are not sufficient data yet to determine if this approach offers any advantages over the use of LAK cells.

The bottom line with all of these studies of IL-2 is whether the response data quoted translate into any benefit for the individual patient either in respect of palliation of symptoms and improved quality of life or increased survival. The former is unfortunately never addressed and the latter is contentious. While improvement in survival compared to historical controls has been shown (Philip *et al.*, 1990), the majority of patients entered into

IL-2 protocols represent a selected group with good performance status.

Finally, a brief mention will be made of non-specific immunotherapy. Marshall *et al.* (1987) showed that coumarin combined with cimetidine gave a response rate of 33% in a group of 42 patients. Since this is similar to the best Il-2 results with only minor toxicity, it will be interesting to see if these results are maintained with larger numbers of patients.

To conclude, what recommendations can be made for the management of the patient with advanced carcinoma of the kidney? The author's opinion is that supportive care only remains a reasonable option for many patients, particularly those with poor performance status and advanced disease. For patients with a good performance status and those requesting treatment, a trial of α interferon given on an out-patient basis is a reasonable approach. An alternative, if available, is IL-2, preferably given subcutaneously to avoid the prolonged in-patient stay. This may give a slightly higher chance of a useful response, albeit at greater cost and toxicity. For poor performance status and elderly patients there is little to be lost by the use of progesterones despite the rather anecdotal response data. Finally, if at all possible, patients should be entered into clinical studies to determine the true effectiveness of these interesting new therapies.

For the future there is a need to carry out randomised studies to compare the efficacy of IL-2 and interferon and to determine if there is any overall improvement in survival for treated patients. In the adjuvant setting it will be valuable to see if IL-2 can reduce the rate of relapse in patients undergoing "curative" nephrectomy. It is possible that its effectiveness may be increased in patients with only microscopic disease. Finally, the growth of molecular biology will no doubt produce new agents for evaluation.

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Prediction of Response to Lithotripsy—the Use of Scanning Electron Microscopy and X-ray Energy Dispersive Spectroscopy

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Summary—A single urine sample was obtained from each of 38 patients before and immediately after treatment with a Wolf Piezolith 2300. Each sample was analysed for crystals using scanning electron microscopy and X-ray energy dispersive spectroscopy. In all cases it was possible to make a stone diagnosis prior to treatment and there was 100% correlation between the pre- and post-treatment diagnosis. All stones smaller than 90 mm^2 on plain X-ray cleared with piezoelectric lithotripsy alone, regardless of composition. Larger stones composed of calcium oxalate were all successfully fragmented, but 5 of 15 mixed or phosphate stones failed to respond.

The planning of lithotripsy sessions would be more efficient if an index of susceptibility of stones to disintegration could be provided prior to treatment. For this, information on the composition of the stones would be desirable. Infra-red spectroscopy is an accurate method of determining stone composition, but this requires stone fragments to be collected by sieving urine. These can only be collected after lithotripsy. A recent study (Bowsher *et al.*, 1990) showed that an accurate stone diagnosis could be made by analysis of crystals in a single post-lithotripsy urine specimen using scanning electron microscopy (SEM) with X-ray energy dispersive spectroscopy (XES).

We have extended the use of these techniques to include examination of a pre-treatment urine specimen, to assess its efficacy in determining the stone composition and to attempt to predict the response to extracorporeal piezoelectric lithotripsy (EPL).

Patients and Methods

Thirty-eight patients, attending for their first lithotripsy session using the Wolf Piezolith 2300, were asked for a single specimen of urine before and immediately after the session. There were 26 males and 12 females, with a mean age of 44 years (range 9–73).

Urine specimens (10–20 ml) were collected directly into plain sterile containers, without sieving, and were analysed (by PC) without knowledge of the clinical details. SEM and XES were used to establish stone composition.

The following details were recorded for each patient:

Whether the stones were single or multiple.
Area of stone on plain X-ray (in mm^2) for solitary stones only.
Whether a prophylactic double pigtail stent was used.
Total number of shock waves delivered.
Stone status on a plain abdominal radiograph 3 months after lithotripsy.

Results

Crystals were detectable in the urine prior to EPL in all cases and there was 100% correlation between the pre- and post-lithotripsy urine specimens. Pure calcium oxalate stones were diagnosed in 22 cases

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(Fig. 1); there were 8 pure calcium carbapatite stones (Fig. 2), 1 cystine stone (Fig. 3), 1 triple phosphate (struvite) stone (Fig. 4) and 6 of mixed composition (Fig. 5).

The composition of the stones and the outcome of EPL treatment at 3 months are tabulated in Table 1. Three months after lithotripsy, 29 patients were stone-free, 4 had shown stone fragmentation but required further treatment for ureteric obstruction and 5 showed no response to EPL after at least 12,000 shock waves (range 12,000–23,500).

Solitary stones

Twenty-four patients had solitary stones. Of these, 18 became stone-free after EPL (75% success rate) (Table 2). Success was dependent upon the size of the stone (Table 3). All 11 stones <90 mm^2 were cleared by EPL alone, regardless of their chemical composition. Of 5 stones between 90 and 139 mm^2 in size, 3 oxalate stones cleared uneventfully, but in 2 cases (1 cystine and 1 oxalate stone) ureteric obstruction was caused by stone fragments. Of 8

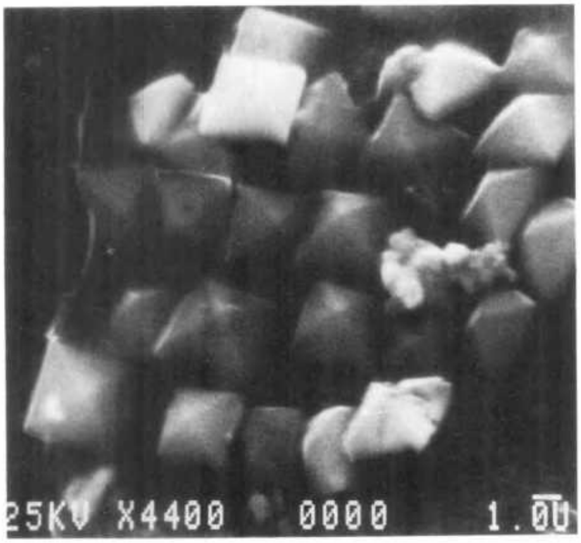

Fig. 1 Oxalate crystals in pre-treatment urine.

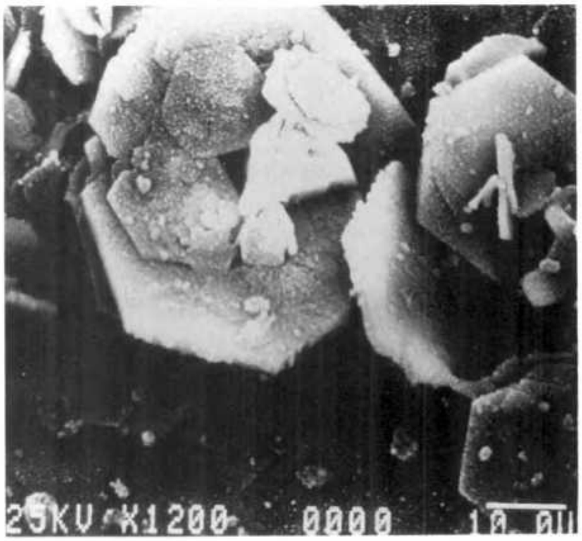

Fig. 3 Cystine crystals in pre-treatment urine.

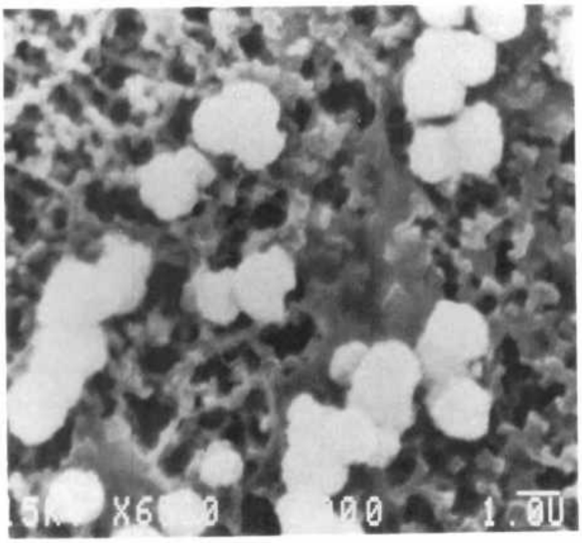

Fig. 2 Carbapatite crystals in pre-treatment urine

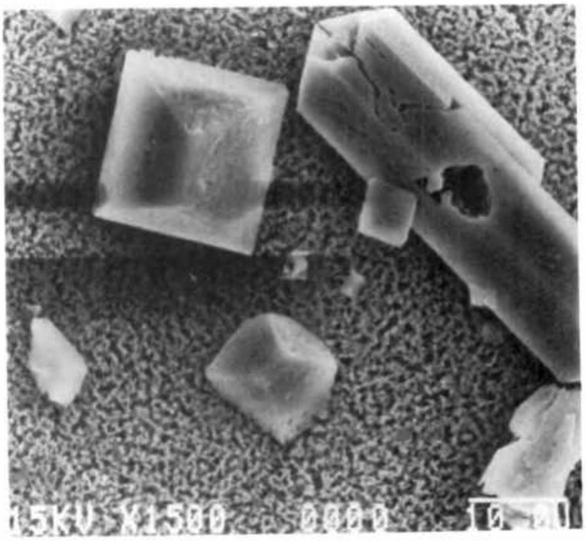

Fig. 4 Struvite crystals in pre-treatment urine

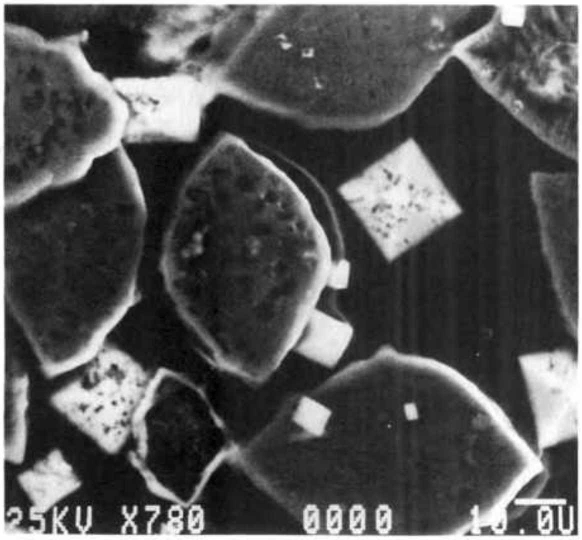

Fig. 5 Mixed uric acid and oxalate crystals in pre-treatment urine.

solitary stones between 140 and 288 mm^2, 4 cleared with EPL (3 oxalate and 1 carbapatite), 1 oxalate stone produced ureteric obstruction by stone fragments, and 3 stones (2 mixed and 1 carbapatite) failed to respond to EPL and required percutaneous nephrolithotomy (PCNL).

Multiple stones

Fourteen patients had multiple stones. Of these, 5 were cases of stone recurrence. Eleven patients were rendered stone-free by EPL (7 oxalate, 1 carbapatite and 3 mixed). One patient required further treatment for ureteric obstruction (oxalate stone) and 2 showed no response to EPL (1 mixed and 1 carbapatite stone) (Table 2).

Successful treatments

Nineteen of 22 patients with pure oxalate stones were stone-free 3 months after EPL, whereas only 10/16 patients with other types of stones were successfully treated with EPL alone. The 29 patients who were stone-free at 3 months received between 2000 and 43,000 shocks to achieve stone clearance. The average number of shock waves per treatment session was 4000. Consequently 18 patients required more than 3 sessions to achieve stone clearance.

Table 1 Outcome of all Stones Grouped by Composition

Stone Composition	*No.*	*Clear at 3 months*	*Ureteric fragments*	*PCNL required*
Oxalate	22	19	3	0
Cystine	1	0	1	0
Carbapatite	8	6	0	2
Triple phosphate	1	1	0	0
Mixed	6	3	0	3
Total	38	29	4	5

Table 2 Comparison of Outcome for Solitary and Multiple Stones

Stone status	*Clear at 3 months*	*Ureteric fragments*	*PCNL required*
Solitary	18	3	3
Multiple	11	1	2
Total	29	4	5

Table 3 Solitary Stones and their Outcome According to Size

Stone size (mm^2)	*Clear at 3 months*	*Ureteric fragments*	*PCNL required*	*Average no. of shocks*
<90	11	0	0	11,555
90–139	3	2	0	14,000
140–288	4	1	3	14,450

Number of shock waves applied to solitary stones

Of the 18 patients with solitary stones who were successfully treated, the average number of shock waves applied was 13,383 (range 4000–28,000). The 3 patients who subsequently underwent PCNL received an average of 18,500 shock waves (range 12,000–23,500), but the 3 patients who needed treatment for ureteric fragments were given only 10,667 shock waves (range 4000–16,000).

Ureteric obstruction—prophylactic stenting

In all, 28 patients were not stented prophylactically (14 with oxalate, 6 with carbapatite, 1 cystine, 1 triple phosphate and 6 mixed stones). Of these, 4 developed ureteric obstruction requiring further treatment. In 3 of these cases the stones were composed of pure oxalate and in the fourth of cystine. The fragments of pure oxalate stones seen in the post-EPL urine tended to be irregularly shaped (Fig. 6), whereas fragments of stones of other compositions were smaller and more rounded.

Discussion

Piezoelectric lithotripsy is an effective treatment for upper urinary tract stones and has the advantage of requiring minimal or no analgesia (Marberger *et*

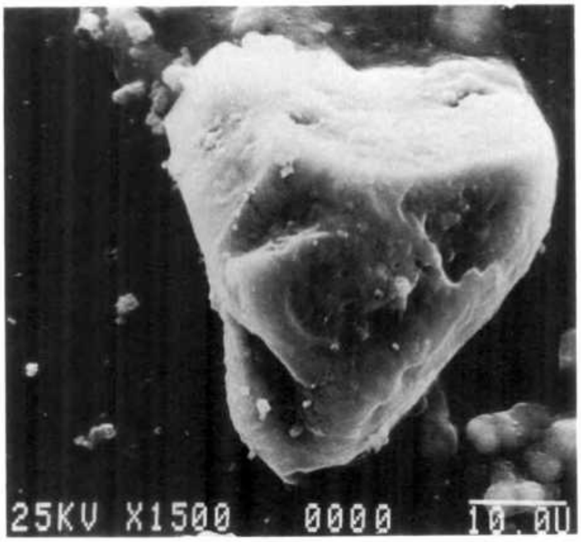

Fig. 6 Fragment of oxalate stone in post-treatment urine.

al., 1988; Vallancien *et al*., 1988). A disadvantage is that EPL is associated with a higher retreatment rate than sparkgap lithotripsy (Bowsher *et al*., 1989; Rassweiler *et al*., 1989). In a particular individual it is difficult to predict how long a course of treatment is likely to last. Furthermore, some stones do not fragment with EPL. Therefore, it would be advantageous to pre-select those patients who would be better treated by other means.

This study has shown for the first time that it is possible to define stone composition on a small specimen of urine *prior to treatment*. It is of importance because the chemical composition of a stone affects the outcome of lithotripsy. Cystine stones have a dense, uniform crystalline structure (Dretler, 1988) which accounts for their relative resistance to lithotripsy (Drach *et al*., 1986; Lingeman *et al*., 1986). Some calcium oxalate stones, in particular those composed of monohydrate, have proved difficult to fragment because of their dense and regular structure. They are associated with a higher retreatment rate than other stones (Dretler, 1988). A recent review has shown that only 11% of patients with brushite stones can be expected to become stone-free by lithotripsy monotherapy alone (Klee *et al*., 1991).

In this series, oxalate stones responded well to EPL, but we did not differentiate the monohydrate from dihydrate forms. However, patients with oxalate stones were more likely to have ureteric stone fragment problems. This may have resulted from differences in the mode of cleavage between oxalate and other stones found by Khan *et al*. (1986), and by the marked preponderance of oxalate stones (>57%) in the present study. Patients with mixed calculi (3/6) and carbapatite stones (2/6) responded poorly to EPL and all 5 patients underwent PCNL. The 3 mixed stones consisted of oxalate/carbapatite in 2 patients and oxalate/uric acid in 1. These stones would be expected to respond well to lithotripsy and their resistance to EPL may be a consequence of differences between piezoelectric and sparkgap fragmentation processes.

Of the 5 patients who required PCNL, 2 had multiple stones and 3 had stones $>140\ \text{mm}^2$. Increasing stone size is known to have an adverse affect on the stone-free rate after lithotripsy, to increase the risk of post-lithotripsy complications and to require an increased number of retreatments (Lingeman *et al*., 1986; Riehle *et al*., 1986). EPL is thought to cause disintegration by a gradual erosive process at the stone surface, yet the number of complications which occur, and the adjuvant procedures which are necessary, are similar to those of patients treated by sparkgap lithotripsy (Rassweiler *et al*., 1989). Treatment with ESWL of stones >2.5 cm is associated with a high risk of complications, but the preliminary insertion of a double pigtail stent can reduce the complication rate from 26 to 7%, and reduces the necessity for auxiliary procedures from 15 to 6% (Libby *et al*., 1988). By using cross-sectional areas from the plain radiographs we found that all small solitary stones $<90\ \text{mm}^2$ responded completely to EPL. An increased risk of complications was apparent in stones of 90 to 139 mm^2 (40%), and only half of the solitary stones $>140\ \text{mm}^2$ were cleared by EPL. Fewer shock waves were applied to those solitary stones which subsequently gave rise to complications from ureteric fragments than to those which responded well (10,667 *versus* 13,383). Incomplete treatment, or the disintegration of oxalate stones into irregular fragments, would explain this finding. The greatest number of shock waves were applied to stones which did not respond to EPL despite repeated treatment sessions (18,500). Patients with these stones would best be treated by other means, rather than have to undergo multiple EPL sessions and yet still require PCNL.

In conclusion, a single pre-treatment urine specimen can be used to identify stone composition. This is advantageous in determining the likely response to EPL, although other factors such as stone size must be considered. Further work is necessary to refine the treatment selection process, and this may involve other methods of stone characterisation.

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Observations on Calcium Oxalate Stone Formers

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Summary—Biochemical studies were performed on 22 adult patients with idiopathic recurrent calcium oxalate renal stone disease and 23 healthy controls. It was found that urinary glutamic-oxaloacetic acid transaminase (UGOT) and urinary glutamic-pyruvic acid transaminase (UGPT) activity was low and lactate dehydrogenase (LDH) and γ-glutamyl transferase (γ-GT) activity was high in the urine of calcium oxalate stone formers. No significant changes were observed in the activity of glutamic-oxaloacetic acid transaminase, glutamic-pyruvic acid transaminase and γ-GT in their blood but a significant reduction was found in both LDH and alkaline phosphatase activity.

It was concluded that the activity of UGOT and UGPT is reduced in patients with kidney stones.

For many years, interest has been focused on urinary abnormalities as a cause of calcium oxalate stone formation. Earlier studies were concerned with the excretion of macromolecules related to their potential nucleating role in the matrix theory of stone formation (Boyce and Swanson, 1955). Recent efforts have been aimed at detecting abnormalities in urinary factors known to affect the degree of saturation of urine with calcium oxalate (Ryall and Marshall, 1983).

Various studies on calcium oxalate stone formation have shown that it is a multifactorial disorder. Among the relevant factors are age, sex, occupation, dietary and fluid intake, geographical location and climate (Anderson, 1969, 1973). In addition, certain metabolic disorders predispose to calcium oxalate formation. There is evidence that urine from healthy persons retards calcium oxalate crystal formation, whereas urine from stone formers has much less inhibitory power (Robertson and Peacock, 1972).

It is known that magnesium, citrate, pyrophosphate and other small ions are effective inhibitors of calcium oxalate crystallisation *in vitro* (Welshman and McGeown, 1972) and that some of the proteins present in urine have been recognised as inhibitors or promoters of kidney stone formation. The presence of other proteins has been reported but have not been correlated with kidney stone formation (Azoury *et al.*, 1982b).

In a previous study, a significant difference was found between the sum of UGOT and UGPT activity in normal subjects and in stone formers (Azoury *et al.*, 1982a) but other investigations have not confirmed this finding. The object of the present study was to demonstrate the possible role of urinary transaminases in calcium oxalate stone formation. It was also considered important to determine whether endogenous enzymes known to be present in urine could be connected with calcium oxalate crystallisation.

Patients and Methods

The study included 22 patients (14 males and 8 females) ranging in age from 25 to 55 years. All had idiopathic recurrent calcium oxalate kidney stone disease and had passed one or more stones yearly. The patients were admitted to the Urology and Nephrology Centre, Mansoura University, and were considered to have normal renal function as demonstrated by normal creatinine levels. Normal controls consisted of 23 volunteers (15 males and 8 females) aged between 20 and 55 years with no history of urolithiasis and without stone disease as judged by radiological techniques.

Blood and urine samples were obtained from all

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participants in a fasting state. An aliquot of the urine was purified by column chromatography filled with Sephadex G 50-150.

Urinary creatinine concentration was determined by the method of Van Pilsum and Bovis (1957). The following enzymes were assayed in the blood serum and purified urine of patients and healthy controls: the activity of glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase was assayed according to Reitman and Frankel (1957). Alkaline phosphatase activity was assayed by the method of Kin and Jegatheesan (1959), while lactate dehydrogenase was assayed kinetically at 37°C according to McQueen (1972). Gamma-glutamyl transferase was assayed kinetically at 37°C as described by Rosalki and Tarlow (1974). Urinary enzyme activity was expressed as u/g creatinine. Statistical analyses were performed according to Snedecor (1956).

Results

Table 1 shows the mean values (±SD) of the activity of glutamic-oxaloacetic acid transaminase (GOT) and glutamic-pyruvic acid transaminase (GPT) in the urine and serum of patients and controls. Significant decreases in both urinary GOT and GPT activity were found in the stone formers but there were no significant changes in the corresponding values of GOT and GPT in the serum of patients when compared with controls. The activity of the lysosomal enzymes LDH, γ-glutamyl transferase and alkaline phosphatase was also determined (Table 2). The activity of LDH was highly significantly elevated in the urine ($P<0.001$) and significantly decreased in the serum ($P<0.01$) of the stone-forming patients. At the same time, γ-GT activity was also significantly increased ($P<0.01$) in the urine of these patients but no significant changes were observed in the serum. In contrast, alkaline phosphatase activity was significantly decreased ($P<0.01$) in the serum of patients with calcium oxalate stone disease.

Discussion

There is considerable evidence from *in vitro* and *in vivo* studies that inhibitors of crystallisation of calcium oxalate are involved in the process of normal and pathological calcification of tissue. These inhibitors seem to be partly absent in stone formers' urine (Azoury *et al.*, 1982b). It is known that L-glutamic acid, L-alanine and L-aspartic acid are present in urine (Azoury *et al.*, 1982a). Patients with idiopathic renal calculi have a lower than normal amino acid content (McGeown, 1957). GOT and GPT convert aspartic acid and alanine respectively to glutamic acid in the presence of α-keto glutaric acid and cofactors.

In a previous study, incubation of stone formers' urine with GOT improved the overall inhibitory potential as reflected by discriminating index measurements, raised glutamic acid levels and decreased aspartic acid concentrations. On the other hand, precipitation was prevented and a correlation was established between the success of treatment and improvement in enzyme activity (Sarig *et al.*, 1985). The results in the present study, namely the significant reduction in both UGOT and UGPT activity in calcium oxalate stone formers, confirm the previous findings of Azoury *et al.* (1984) and this lack of UGOT and UGPT

Table 1 Activity of Glutamic-oxaloacetic Acid Transaminase (GOT) and Glutamic-pyruvic Acid Transaminase (GPT) in Urine (u/g creatinine) and Blood Serum (u/ml)

	Urine		*Blood serum*	
	Controls	*Patients*	*Controls*	*Patients*
GOT				
Mean ± SD	16.78 ± 8 48	10 36 ± 6.99	5 30 ± 2.85	5.70 ± 3.48
No	23	22	23	22
P		<0 05		>0 05
GPT				
Mean ± SD	14.00 ± 8.22	9.68 ± 4 68	4 90 ± 2.65	5.10 ± 2.51
No	23	22	23	22
P		<0.01		>0.05

$P > 0.05$ = Not significant.
$P < 0.05$ = Significant.
$P < 0.001$ = Highly significant

Table 2 Activity of Lactate Dehydrogenase (LDH), γ-glutamyl Transferase (γ-GT) and Alkaline Phosphatase (Alk-ase) in Urine (u/g creatinine) and Blood Serum (u/ml)

	Urine		*Blood serum*	
	Controls	*Patients*	*Controls*	*Patients*
LDH				
Mean+SD	6.86±2.28	20.70+9.05	128 38±34.07	89.23±28.51
No.	23	22	23	22
P		<0.001		<0 01
γ-GT				
Mean±SD	44.43±21 46	58.13±22.08	43.90±14.61	50 40±16.06
No	23	22	23	22
P		<0.01		>0.05
Alk-ase				
Mean±SD	34 51±22.37	36.87±31.07	77.09±21.34	67.45±26 85
No.	23	22	23	22
P		>0.05		<0.01

$P > 0.05$ = Not significant.
$P < 0.05$ = Significant.
$P < 0.001$ = Highly significant.

activity may be one of the causes of the low inhibition/retardation effect of stone formers' urine and consequent calcium oxalate stone formation. If this finding is confirmed in other centres, it could possibly indicate that one of the possible retardation mechanisms of calcium oxalate stone formation may involve L-glutamic acid which forms *in vivo* due to UGOT and UGPT activity. Healthy people have considerable UGOT and UGPT activity which may retard the calcium oxalate crystal growth rate via L-glutamic acid produced *in situ* and thus prevent stone formation. This mechanism would appear to be deficient in stone formers. Some confirmation of this observation is obtained by the claim that successful stone treatment using DL-alanine (Chow *et al.*, 1975), which by itself does not retard calcium oxalate precipitation, can be explained by transformation of alanine into glutamic acid by UGPT and the subsequent activity of this acid in urine.

To address whether renal tubular dysfunction is present in patients with calcium oxalate stones, LDH, γ-GT and alkaline phosphatase were measured in urine and blood. Table 2 shows that patients with calcium oxalate stone disease have elevated urinary excretion of both LDH and γ-GT, which suggests tubular damage, but the crucial point is whether this damage is primary or secondary to renal stone disease. A parallel study in the rat showed that calcium oxalate loading can promote increased urinary excretion of such enzymes (Baggio *et al.*, 1983). These authors demonstrated that if this damage is primary it may be viewed as a promoting factor in urolithiasis and if it is secondary it might be considered a factor capable of increasing crystal deposition. Moreover, Gill *et al.* (1979) demonstrated that injury to the urothelial surface can promote aldhesion and growth of crystals.

The inhibition of both LDH and alkaline phosphatase activity in the serum of patients with calcium oxalate renal stones has no known or reasonable correlation to stone formation and further studies are necessary to investigate this finding.

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Treatment of Stones in Caliceal Diverticula: Extracorporeal Shock Wave Lithotripsy versus Percutaneous Nephrolitholapaxy

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Summary—Stones in caliceal diverticula may cause symptoms for which treatment is indicated. Both extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolitholapaxy (PNL) are recommended.

We have evaluated the results of ESWL treatment of stone-containing caliceal diverticula and compared these with the results obtained by percutaneous surgery.

In the ESWL group, 15 patients were treated with an electromagnetic lithotriptor (Siemens Lithostar). After 3 months, plain abdominal X-rays revealed that only 2 patients were both stone-free and symptom-free. Of the 13 patients with residual fragments, 7 had no symptoms. The remaining 6 were treated by a lower pole resection (n=3), a percutaneous procedure (n=2) and long-term administration of antibiotics (n=1).

Sixteen patients were treated percutaneously. Puncture failed in 3 and they underwent a lumbotomy. In the remaining 13 patients the stones were reached by direct puncture (n=12) or via an adjacent calix (n=1). After 3 months, 10 patients were stone-free and had no symptoms. Morbidity consisted of post-operative bleeding (n=3) and high fever (n=1). It was concluded that caution should be exercised in the treatment of stone-containing caliceal diverticula. Only in symptomatic cases is treatment indicated and ESWL is the first choice. If ESWL fails (residual stones and persistent symptoms), PNL should be performed, although it is associated with a higher morbidity rate.

Extracorporeal shock wave lithotripsy (ESWL) has gained worldwide acceptance as the treatment of choice for urinary tract calculi. Approximately 90% of all calculi can be treated effectively by this method (Chaussy, 1988).

A pyelocaliceal diverticulum has a typical radiological appearance and is probably of congenital origin (Wulfsohn, 1980). Caliceal diverticula are found on routine intravenous urography (IVU) in less than 4.5/1000 IVUs (Middleton and Pfister, 1974; Timmons *et al.*, 1975; Wulfsohn, 1980). Although the symptoms may resemble those of a hydrocalix, it is a different condition. Diverticula are found in the corticomedullary area (Wulfsohn, 1980). They may contain calculi and cause symptoms such as haematuria, renal colic or urinary tract infection, for which treatment is indicated (Abeshouse and Abeshouse, 1963).

Psihramis and Dretler (1987) advocated ESWL as the best treatment for stones in caliceal diverticula. All calculi were fragmented but spontaneous evacuation occurred in only 20% of cases.

ESWL is relatively contraindicated in the case of an obstruction below the calculus, which is the case in caliceal diverticula. The caliceal neck might hinder spontaneous passage of stone fragments (Wilbert *et al.*, 1987; Thürhoff and Alken, 1988) and other authors therefore recommend percutaneous removal as the primary treatment, since the stone can be removed completely and the narrow caliceal neck can be dilated during the same procedure in order to prevent or delay recurrence (Hulbert *et al.*, 1986; Thürhoff and Alken, 1988).

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However, percutaneous surgery may have serious complications (Van Cangh *et al.*, unpublished observations).

In view of this controversy we have retrospectively evaluated the results of ESWL for caliceal diverticula calculi and compared them with the results obtained by percutaneous surgery.

Patients and Methods

We reviewed the case records of patients with stone-containing caliceal diverticula treated with ESWL or PNL. Caliceal diverticula were defined according to Wulfsohn (1980): eventrations of the upper collecting system lying within the renal parenchyma and communicating with the main collecting system via a narrow channel (caliceal neck) (Fig.). A full history was taken and all patients underwent a physical examination, laboratory investigations, urine culture and intravenous urography. Thirty-one symptomatic patients were treated—16 (6 males and 10 females) by PNL between 1986 and 1988 and 15 (6 males and 9 females) by ESWL after January 1988 because at that time a lithotriptor (Siemens Lithostar) was installed. All patients treated percutaneously had a general anaesthetic. A 7 F ureteric catheter was inserted and artificial hydronephrosis created. The patient was then placed in the prone position and puncture of the stone-containing calix was performed using both ultrasound and fluoroscopy. A guide wire was inserted and the percutaneous tract was dilated up to 30 F. The stone was removed by forceps and, if possible, the caliceal infundibulum was identified and dilated up to 12–16 F. A multiholed balloon nephrostomy catheter (12 F) was left in place for 3–6 weeks to allow the dilated infundibulum to heal. Patients were hospitalised for at least 3 days.

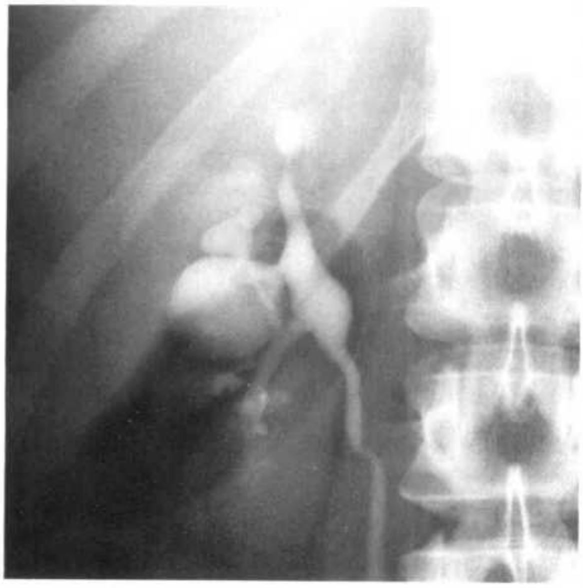

Fig. Typical appearance of a kidney with caliceal diverticula.

All 15 ESWL patients were treated on an outpatient basis. The technique of electromagnetic ESWL has been described by Wilbert *et al.* (1987). Patients were followed up 2 weeks, 1 month and 3 months after treatment. Postural drainage was advised in all cases. Twelve of the 31 patients had a urinary tract infection and were treated with antibiotics for at least 5 days. In the case of sterile urine (n = 19), patients received antibiotic prophylaxis for 1 day.

Results

Patients' symptoms at presentation are listed in Table 1. Hypertension or decrease in kidney function was never an indication for treatment.

Table 2 shows the site of the stones. The average stone size in patients treated by ESWL was 94 mm^2. In the first ESWL session an average of 3500 shocks was given (range 1200–4000) at 18.1 kV. During treatment, 7 patients required analgesia (intravenous fentanyl citrate, maximum dose 0.1 mg). Within 3 months, 3 patients underwent a further ESWL session because of persistent symptoms. Transient haematuria and ecchymosis occurred in all patients, but no other side effects were encountered (Table 3). The average treatment time (including preparation of the patient and post-ESWL care)

Table 1 Symptoms at Presentation

	No. of patients	
	ESWL	*PNL*
Pain	12	13
Infection	4	8
Haematuria	3	—

Table 2 Stone Localisation

	ESWL	*PNL*
Upper calix	6	5
Middle calix	1	4
Lower calix	8	7

Table 3 Results and Complications of Treatment

	ESWL	*PNL*
Complications		
Haematuria	15	—
Ecchymosis	15	—
Access failed	—	3
Post-operative bleeding	—	3 (1 serious)
Symptom-free	9 (60%)	10 (80%)
Stone-free	2 (13%)	10 (80%)

was 95 min (range 75–115). X-ray exposure time ranged from 0.4 to 1.8 min (average 1.3).

After 3 months plain abdominal X-rays revealed that only 2 patients were free of stones and had no further symptoms. The diverticula of 13 patients still contained stone fragments: in 7 cases the stone size was reduced by ESWL and in 6 cases ESWL had no effect. However, of these 13 patients with residual fragments, 7 had no further symptoms. In the remaining 6 patients with persistent symptoms a lower pole resection was performed in 3 cases and percutaneous stone removal with dilatation of the caliceal neck was successful in 2. The last patient received long-term antibiotic treatment (Table 3).

In the PNL group, most patients suffered pain and urinary tract infection. The causative microorganisms were *Proteus mirabilis* (n = 5), *Escherichia coli* (n = 2) and *Staphylococcus aureus* (n = 1).

In 3 patients the caliceal diverticulum could not be punctured directly and they were treated by open surgery.

In the 5 patients with caliceal diverticula in the upper pole, puncture was performed between the eleventh or twelfth rib. In 11 patients 1 puncture was effective but a second puncture was required in 2 cases. In 1 patient the diverticulum could not be punctured directly and access to the renal collecting system was achieved by puncture of an adjacent calix. In this patient the caliceal neck could not be identified and the stone had to be left *in situ*.

In 10 patients the stones were extracted successfully by means of forceps. In 2 patients small stone fragments were left behind. Of these 12 patients, the caliceal neck was identified in 9 and passed with a guide wire, after which dilatation to 12–16 F was performed. A 12 F nephrostomy catheter was left *in situ* for 3–6 weeks. In 3 of 12 patients the caliceal neck could not be identified; the wall of the diverticulum was coagulated, resulting in blockage of the connection to the renal collecting system. This technique has been recommended by Wulfsohn (1980), especially if little or no surrounding renal parenchyma is present.

Treatment time (excluding preparation of patients and post-operative care) ranged from 60 to 120 min (average 115). The average X-ray exposure time was 5.5 min (range 3.6–7.2).

In addition to failed puncture in 3 patients, resulting in open surgery, complications consisted of post-operative bleeding in 3 patients, for which 2 required packed cells. The bleeding could not be stopped in 1 patient and selective embolisation of the bleeding artery was performed. Another complication was post-operative fever (>39.5°C) in 1 patient which was treated successfully with antibiotics. Among the 5 patients who were punctured intercostally, the procedure caused neither pneumothorax nor hydrothorax. No TUR syndrome occurred. Hospitalisation ranged from 3 to 21 days (average 6.7).

Ten of the 13 patients were stone-free and symptom-free after a follow-up of 3 to 36 months (mean 18). The 3 remaining patients had residual stones and intermittent flank pain, treated with analgesics.

Recurrent stone formation was seen in 3 patients after an average of 21 months.

Discussion

Caliceal diverticula calculi require treatment in the case of chronic or recurrent pain, urinary tract infection or progressive renal damage (Timmons *et al.*, 1975; Hulbert *et al.*, 1986). In certain cases, tuberculosis should be excluded before commencing treatment (Wulfsohn, 1980).

Traditionally, treatment has included surgical extraction of the calculus, closure of the communicating tract and obliteration of the diverticulum by marsupialisation and fulguration. Alternatively, partial or total nephrectomy has been advised (Wulfsohn, 1980; Hulbert *et al.*, 1986), but with the introduction of PNL, and more recently ESWL, these treatments are now obsolete (Thürhoff and Alken, 1988).

Symptomatic caliceal diverticula containing calculi are uncommon and therefore it is difficult to recruit large numbers of patients.

Reports on the treatment of caliceal diverticula calculi with ESWL have shown that the success rates (both stone-free and symptom-free) range from 20 to 50% (Psihramis and Dretler, 1987; Ritchie *et al.*, 1990; Wilbert *et al.*, 1990). According to this definition, the success rate in the present series was only 13%, but comparison with other series is not statistically valid because of differences in the selection of patients and the small numbers studied in each group. However, if we do compare our results with those of other authors and take into account the re-treatment rate, our results are comparable (Table 4).

After ESWL treatment, 60 to 75% of patients can be symptom-free (Psihramis and Dretler, 1987; Ritchie *et al.*, 1990; Wilbert *et al.*, 1990).

As caliceal diverticula are lined by non-secretory transitional epithelium, they contain urine that is derived by filling from the adjacent collecting system (Hulbert *et al.*, 1986). Urinary stasis, particularly in patients with a history of urolithiasis, will theoretically result in stone recurrence. In patients with urinary tract infections due to urease splitting bacteria, persistent symptoms and stone growth can occur if residual fragments remain in the diverticula. Although 7 of 13 patients with residual stones in the ESWL group had no symptoms after treatment, 3 of the remaining 6 patients underwent a lower pole resection because of persistent symptoms.

ESWL treatment is non-invasive and can be performed on an out-patient basis with either minimal anaesthesia or none at all, but its effectiveness for caliceal diverticula calculi is doubtful. So far, no long-term follow-up studies have been reported with regard to stone recurrence, but we believe that ESWL will seldom lead to permanent success.

The alternative to ESWL is a percutaneous procedure (Hulbert *et al.*, 1986; Thürhoff and Alken, 1988), when both the cause of stone formation and the stone itself can be treated, and it should therefore be regarded as a more definitive measure. Three months after percutaneous treatment, 80% of our patients were both stone-free and symptom-free (Table 5). However, these figures are biased because of the different techniques applied and the lack of data.

The disadvantages of the percutaneous approach, when compared with ESWL, are the need for general anaesthesia, hospitalisation and the relative high complication rate (especially in punctures above the eleventh rib). In 22 patients treated by PNL, Van Cangh *et al.*(unpublished observations) found major complications in 3, such as arteriovenous fistula and hydrothorax. We had 3 cases of post-operative haemorrhage and in one case selective embolisation had to be performed.

After PNL treatment, obliteration of the diverticulum was found in 3 patients and 3 developed recurrent stones within an average of 21 months.

Several techniques have been used to reduce the complication and stone recurrence rates. If overlying parenchyma is present the caliceal neck should be dilated and intubated for 1 to 3 weeks in order to minimise loss of kidney function and decrease the complication rate (Thürhoff and Alken, 1988). If almost no overlying parenchyma is present, the narrow caliceal neck should be closed by fulguration and complete exteriorisation achieved by resection of the roof (Wulfsohn, 1980) Hulbert *et al.* (1986) reported that in 5 of 7 patients IVU showed obliteration of the diverticulum 3 to 14 months after direct puncture and van Cangh *et al.* (unpublished observations) could not visualise the diverticulum post-operatively in 80%. Thus fulguration of the diverticulum wall after stone removal could be

Table 4 ESWL: Results after 3 Months in Relation to Re-treatment Rate

	No. of patients	*Re-treatment rate*	*Stone-free rate (%)*	*Symptom-free rate (%)*
Psihramis and Dretler (1987)	10	30	20	70
Wilbert *et al.* (1990)	16	0	20	–
Ritchie *et al.* (1990)	20	100	25	75
van Cangh *et al.* (unpublished data)	27	45	50	75
Present series	15	0	13	60

Table 5 Results of Percutaneous Treatment

	No of patients	*Stone-free (%)*	*Symptom-free (%)*
Hulbert *et al* (1986)	10	?	?
Thürhoff and Alken (1988)	16	94	?
van Cangh *et al.* (unpublished data) (1990)	22	90	100
Present series	16	80	80

a more effective way of reducing recurrent stone formation. Unfortunately, as with comparison of treatment results, the complication rates of the various techniques cannot be compared.

In conclusion, we believe that ESWL should be the treatment of choice in caliceal diverticula because of its non-invasiveness, although a high failure rate must be accepted and its long-term effect is questionable. Percutaneous treatment is more effective in rendering the patient stone-free and in reducing symptoms, but it has a higher complication rate and should therefore be reserved for patients with persistent symptoms after ESWL.

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Clinical Study of Patients with Renal Carcinoma Surviving for more than 10 Years after Nephrectomy

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Summary—Of 207 patients with renal carcinoma we studied 50 who survived for more than 10 years after nephrectomy. These 50 patients were younger than the others at the time of operation and included more females. They had lower stage and lower grade tumours. Recurrence was detected in 18/50 patients and 6 died from cancer. Recurrence developed approximately 10 years after nephrectomy. Eleven patients with recurrences had metastases to a single organ and 9 received multidisciplinary treatment, mainly surgery and radiotherapy.

The survival rate 10 years after nephrectomy was lower in patients with recurrences than in those without recurrent tumours and there was a significant decrease in the survival rate 17 years after nephrectomy. Although the patients had low grade and low stage tumours 10 years after nephrectomy, careful follow-up is recommended in such cases as it is possible that they may have dormant tumours.

As with many other malignant tumours, renal carcinoma tends to metastasise soon after surgery (Onshi *et al.*, 1984), but recurrences can develop more than 10 years after nephrectomy. These patients with late recurrences present a clinical problem (McNichols *et al.*, 1981; Satomi *et al.*, 1984). We have studied the clinical characteristics of patients who survived for more than 10 years after nephrectomy, especially those with late recurrences.

Patients and Methods

Of 207 patients with renal carcinoma who were treated at Jikei University Hospital and affiliated institutions between January 1957 and December 1981, 50 (24.2%) survived for more than 10 years after nephrectomy and they comprise our study group.

In addition to nephrectomy, 25 of these 50 patients underwent lymph node dissection (in right-sided cases the nodes extending from the crus of diaphragm to the bifurcation and around the inferior vena cava and aorta were removed: in left-sided cases the para-aortic region was dissected).

No patient in the study group underwent nephrectomy in the 1950s, but 8 of 35 patients (23%) had a nephrectomy in the 1960s, 38 of 143 (26.6%) in the 1970s and 4 of 23 (17%) in 1981 (Fig. 1).

The following studies were performed:

(1) The clinical background data on the 50 study group patients (Group 1) were compared with similar data on the remaining 157 patients (Group 2).
(2) In Group 1, the clinical characteristics of patients who developed recurrences were compared with the characteristics of those who did not.
(3) The clinical features of patients with late recurrences were examined.

The classification of Robson *et al.* (1969) and the 4-grade system of Bannayan and Lamm (1980) were used to stage and grade the tumours. Statistical differences were analysed by the Z test and correlations by the *t* test. Survival rates were calculated by the Kaplan-Meier method and differences were assessed by the generalised Wilcoxon method.

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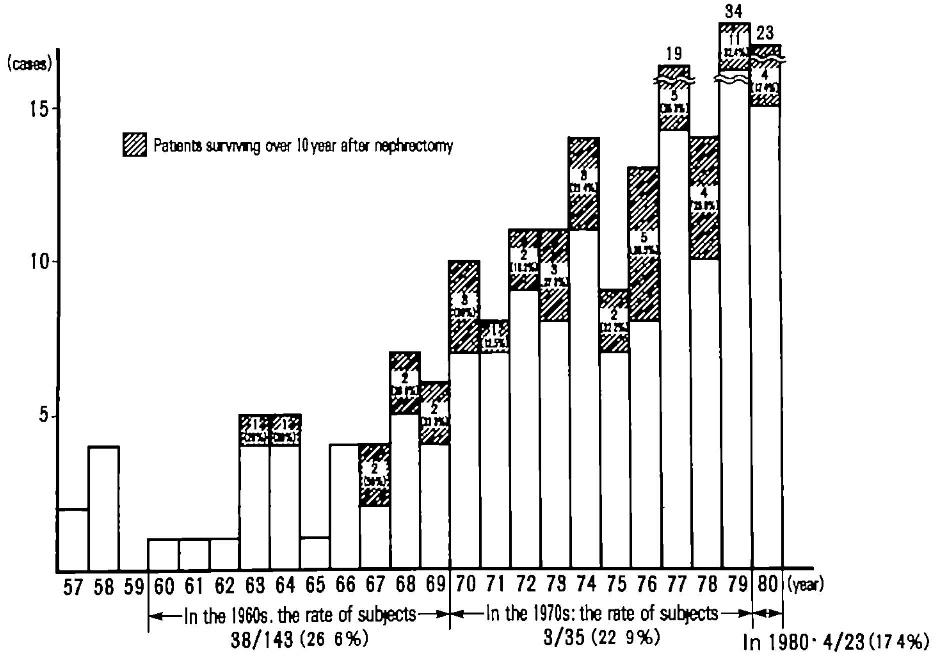

Fig. 1 Patients surviving for more than 10 years after nephrectomy according to age.

Results

Clinical background data

Clinical features concerning patients (host factors). The age of Group 1 patients at the time of operation ranged from 28 to 70 years (median 53), and the median age of Group 2 patients was 57 years. Group 2 included more male patients (male to female ratio = 3.0:1) than Group 1 (male to female ratio = 1.1:1.0). There was a statistically significant increase in the ratio of females in Group 1 ($P < 0.01$, confidence coefficient = 3.0902, Z = 3.0996) (Table 1).

With regard to the latent period between the appearance of symptoms and initial presentation, there were no significant differences between the 2 groups. The urinary tract symptoms were recognised in 47/50 patients (94%) and in the 3 others tumours were found incidentally. The most common symptoms were haematuria (macroscopic and microscopic) in 41 cases (82%) and pain in 10 (20%). There was no major difference in symptoms between the 2 groups (Table 1).

Clinical features of the tumour (tumour factors). The diameter of the tumours was a minimum of 2 cm and a maximum of 17 cm (median 6.3) in group 1

Table 1 Clinical Background

Comparative items	*Group 1 (n = 50)*	*Group 2 (n = 157)*
(1) *Host factors*		
Age at operation (years)	28–70	30–83
(median)	(53)	(57)
Sex (male.female)	26.24*	118:39*
(ratio)	(1 1·1)	(3.0:1)
Affected side (left:right)	24:26	80:77
Time from appearance of symptoms to medical consultation	1 day–3 years	1 day–2 years 4 months
(median)	(16 days)	(19 days)
Chief complaints		
(i) Symptomatic	(n = 47)	(n = 155)
Haematuria	41 (82%)	131 (85%)
Pain	10 (20%)	14 (9%)
Palpable mass	3 (6%)	8 (5%)
Others	4 (8%)	2 (1%)
(ii) Incidental	3 (6%)	2 (1%)
(2) *Tumour factors*		
Tumour size (cm)	2.0–17.0	2 4–15 5
(median)	(6 3)	(6.9)
Stage	46·4*	80.77*
(low:high)	(11.5:1)	(1.04:1)
Grade	44·6*	76·72*
(low:high)	(7.3·1)	(1.1·1)

*$P < 0.001$

and no significant difference was detected between the 2 groups. Stage I tumours were recorded in 35 patients (70%), stage II in 11 (22%) and stage IIIA in 4 (8%). Histological grade I was recorded in 20 patients (40%), grade II in 24 (48%) and grade III in 6 (12%). Thus most patients in group 1 had statistically significant low stage tumours ($P<0.001$, confidence coefficient=3.7194, Z=5.1796) and also low grade tumours ($P<0.001$, confidence coefficient=4.2671, Z=4.9403) (Table 1).

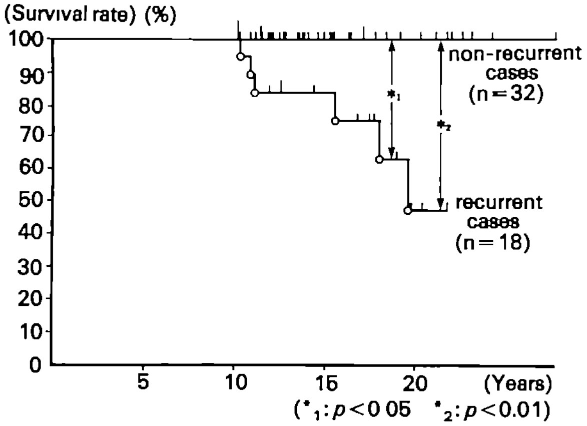

Fig. 2 Comparison of survival rate between patients with and those without recurrent tumours.

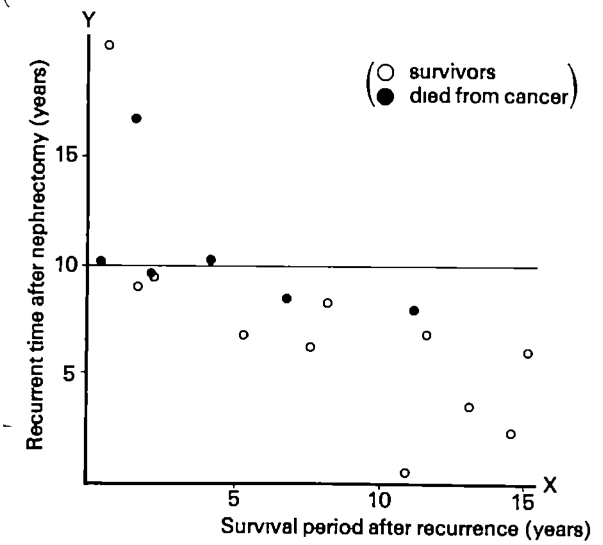

Fig. 3 Relationship between time of recurrence and duration of survival.

Comparison of clinical characteristics in patients with recurrent tumours and those without recurrences

No significant difference was observed between the 2 groups regarding age at operation, sex, affected side and tumour size.

Survival. In group 1, follow-up after nephrectomy ranged from 3662 to 9975 days (median 5485); 39/50 patients (78%) were alive on 31 December 1990) and 11 (22%) survived for more than 10 years. Six of these 11 patients died from cancer and 5 from other diseases. There were 32 patients (64%) without recurrent tumours and 18 (36%) with recurrences.

Follow-up ranged from 3665 to 8753 days (median 5348) in patients without recurrences and from 3875 to 7836 days (median 5624) in those with recurrences. No significant difference was observed between the 2 groups. However, the survival rate decreased after 10 years post-operatively in the recurrent group and a significant difference was observed 17 years after nephrectomy between the 2 groups (Fig. 2).

Stage and grade distribution. Low stage tumours (I and II) predominated (94% in the non-recurrent group and 83% in the recurrent group), as did low grade tumours (94% in the non-recurrent group and 72% in the recurrent group). No significant difference was observed between the 2 groups in terms of stage and grade.

Clinical features of patients with late recurrences

Recurrent times after nephrectomy and survival time after recurrences. Recurrences occurred a minimum of 1 year and 3 months and a maximum of 19 years after nephrectomy (median 8 years 6 months). Duration of survival after recurrence ranged from 8 months to 15 years 2 months (median 6 years 10 months). A minus dependency was observed between the recurrent times after nephrectomy and the survival time after recurrence. The equation was expressed as $Y=4396.76-0.546851\ X$ (correlation coefficient=−0.740121, t value=3.66621) (Fig. 3).

Comparison between patients who died from cancer and those who survived among those with recurrences. Comparison of the number of organs with metastases and the number of individual metastases showed that there was only one patient with a single metastasis to a single organ who died from cancer. Five of 6 patients had multiple metastases or metastases to multiple organs among those who

Table 2 Comparison between Patients who Died from Cancer and Those who Survived

Patients who died from cancer (n=6)	*Survivors (n=11)*
(1) Metastatic organs and metastatic foci	
(i) Solitary organ	
Solitary focus: 1 case (16.7%)*	3 cases (72.7%)*
Multiple foci: 2 cases (3.33%)	3 cases (27.3%)
(ii) Multiple organs 3 cases (50.0%)	no case
(2) Metastatic organs and treatment	
(i) Solitary organ	
Solitary focus: lung, IFN→op→IFN→op→op→!	lung; 5-FU (C.R.) lung; 5-FU (C.R.) lung, IFN→(N.C.)→IL-2+ra (N.P) brain, op→lung→op→LN→op→LN→op (N.P) LN, op (N.P.) contralateral adrenal gland; →op→LN→op (N.P.) renal bed, op (N.P.) pancreas; op (N.P.)
Multiple foci: lung, IFN→! lung; FAV→!	lung, MFC+ra (N.P.) lung, 5-FU (N.C.)→op (N.P.) bone, IFN+ra (P.D.)
(ii) Multiple organs	
lung+liver, MACV→! lung+liver+bone+LN, MACV→! contralateral kidney+bone; IFN→!	no case
(one patient died from myocardial infarction in the recurrent cases)	

LN lymph-node metastasis IFN: interferon. IL-2: interleukin-2. MFC: mitomycin C+5-FU+cytocine arabinoside MACV. methotrexate+actinomycin D+cyclophosphamide+vincristine. FAV: 5-FU+Adriamycin+vinblastine. ra: radiotherapy op: surgical resection. C.R.: complete response. N.C.. no change. P.D.. progressive disease. N.P · no evidence of progression. !. cancer death.

*· P<0.016.

died from cancer, while 8 of 11 survivors had single-organ metastases or only one metastasis. Thus significantly more patients who survived after recurrence had single-organ metastases or only one metastasis ($P<0.016$, confidence coefficient= 2.1973, Z=2.2106) (Table 2).

With regard to the sites of metastasis and the method of treatment, systemic chemotherapy (including immunotherapy) was given to all those who died from cancer except for one patient with single metastases who underwent resection of metastatic lesions in the lungs 3 times. Among the survivors, 6 underwent resection of metastases, 2 received chemotherapy alone and the remainder were given combination treatment. The metastases disappeared in the 2 patients who received chemotherapy (5-FU) alone (Table 2).

Discussion

Renal carcinoma tends to metastasise early if the tumour has a high degree of histological malignancy (Sella *et al.*, 1987). On the other hand, late recurrences can develop more than 10 years after nephrectomy (McNichols *et al.*, 1981; Satomi *et al.*, 1984). Satomi *et al.* (1984) classified the former group of tumours as the "quick type" and the latter as the "slow type" and emphasised the need to establish effective adjuvant therapy for renal carcinoma and long-term follow-up after nephrectomy.

In this study we investigated the clinical course of 207 patients with renal carcinoma and found that 50 (24.2%) survived for more than 10 years after nephrectomy. The 10-year survival rate has been previously reported as 30.5 to 38% (Skinner, 1971; McNichols *et al.*, 1981; Nurmi, 1984; Satomi *et al.*, 1984).

The clinical characteristics of our long-term survivors included a younger age at the time of surgery and a higher percentage of females, while the tumours were lower stage and grade. McNichols *et al.* (1981) reported that the age at diagnosis of patients with recurrences appearing over 10 years after nephrectomy was 53 years. Patients with late recurrences tended to be younger than the average 55.3 years. Lieber *et al.* (1981) reported that there was no relation between the age at diagnosis and survival. However, Satomi *et al.* (1988) found that many long-term survivors were aged less than 40 years.

Our results and those of McNichols *et al.* (1981) and Lieber *et al.* (1981) have shown a high percentage of females among long-term survivors. The reasons for this are unclear, but Lieber *et al.* (1981) assumed that a difference in the hormonal environment might be involved, because receptors for androgens, oestrogens and progesterone are present on renal carcinoma cells.

It is obvious that the stage of the tumour at the time of treatment and the histological grade of the primary tumour are important prognostic factors. In the present series, approximately 90% of Group 1 patients had low stage, low grade tumours.

Post-operative recurrences were observed in 18 of the long-term survivors in this study. The recurrences appeared at intervals ranging from 1 year 4 months to 19 years post-operatively. An investigation of the timing of recurrences among the 6 patients who died from cancer revealed that all except 1 developed recurrences approximately 10 years post-operatively. This shows the importance of long-term follow-up of patients with renal carcinoma and the need to establish effective adjuvant therapy.

Appelqvist (1984) reported a 5-year survival rate of 32% for renal carcinoma patients who underwent surgery to remove a single metastatic focus, but this rate increased to 58.3% in patients in whom complete resection was possible, indicating that surgical treatment should be performed for a single metastasis if radical resection is possible (O'Dea *et al.*, 1978).

Most of the recurrences in our patients were in the lungs. Thrasher *et al.* (1990) reported that if there are less than 4 lung metastases, surgery is indicated even in patients with metastases in both lung fields.

Radiotherapy is often administered to recurrent tumours and Seitz *et al.* (1988) reported that localised radiotherapy to the distant metastatic foci (mainly in bone) not only alleviated local symptoms, but also prolonged survival. It was previously thought that irradiation had an immunosuppressive action, but Ogawa *et al.* (1986) showed that low doses of irradiation had a local immuno-potentiating effect. It may be worthwhile to use radiation concomitantly with interferon and interleukin-2.

The present study has indicated that one must consider the possibility of late recurrence at all times and the same strict treatment protocol should be used for both early and late recurrences. At the same time, it must not be forgotten that follow-up should be continued for more than 10 years post-operatively.

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Does Too Much Urology Damage Your Eyesight? Study of Macular Function

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Summary—A study comparing the macular function of both eyes of 130 urological surgeons was carried out to investigate whether the increased light exposure to the endoscoping eye caused any deterioration of macular function. The non-endoscoping eye was used as a control.

A sophisticated computer test of colour contrast sensitivity was used. The computer assesses the degree of brightness at which the subject is just able to detect a coloured grating, and for each eye this is expressed as a threshold for the red/green axis and the blue/yellow (tritan) axis. The subjects also completed a questionnaire about their working patterns and their general and ophthalmic history and had a brief examination of the fundus.

The results do not suggest that urologists are suffering any significant macular damage as a result of their work with endoscopes.

Method

The investigators attended 2 major urological conferences held in June 1991—the Ninth World Congress on Endourology and ESWL/Seventh Research Symposium on ESWL in Vienna, June and the British Association of Urological Surgeons' Annual Meeting in Glasgow.

In all, 130 urologists were examined.

Each subject was asked to complete a questionnaire before undergoing the test of colour contrast sensitivity and a brief ophthalmic examination was then carried out. Subjects with a history of pathology in either eye and those who were colour blind were excluded from the study.

Questionnaire

Details were recorded regarding the age of the subject and the racial origin (as the degree of eye pigmentation is known to be significant in the aetiology of macular disorders) (Weiter *et al.*, 1985). Any symptoms of difference between the 2 eyes were noted, together with practical details with regard to surgical experience, *i.e.* the number of years the urologist had been exposed to endoscopy and the number of hours a week the surgeon practised. We also asked which eye was routinely used and which was the dominant hand. Details were recorded of past ophthalmic history and family history of eye disease. Relevant past medical history was obtained, *e.g.* diabetes, hypertension and treatment with drugs known to affect visual function. Finally, hobbies which involved high light exposure were recorded as these were thought to have a possible influence on the results.

Computer test of colour contrast sensitivity

A specially designed computer test was used which involved responding to changes on a colour viewing screen divided into 4 quadrants. Each eye was tested twice, in the order RLLR and LRRL to counterbalance the effects of practice and fatigue. The screen displayed either a red/green or a blue/yellow (tritan) colour grating at any one time, varying in intensity around the individual's threshold level.

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The subject was carefully instructed and given 15 practice trials before commencing the test. Each test consisted of approximately 35 trials. On each trial an auditory tone was given to indicate that a stimulus was about to be presented in 1 of the 4 quadrants, the overall luminance being held constant. The stimulus was displayed for 2 s and then gradually removed. The subject's task was to press 1 of 4 buttons corresponding to the 4 quadrants of the display, indicating the quadrant which contained the stimulus. The subject was required always to make a guess on the best available evidence, even on those occasions when he or she felt unable to see the stimulus.

The threshold for a given colour grating was estimated by averaging the 2 test results for each eye.

Ophthalmic examination

Iris colour was observed and recorded as either light, medium or dark. Pupils were checked for normal responses and it was recorded if the subject wore spectacles and if a tint was incorporated. Degree of accommodation was measured using the RAF rule. A brief fundal examination was performed to exclude obvious opacification of the ocular media and to view the macula and disc.

Results

Data were collected from 123 urologists who had fulfilled all of the criteria, completed the questionnaire and performed the test.

Differences between eyes

The data were examined to see whether there was any evidence of significantly poorer vision in the endoscoping eye, the null hypothesis being that there was no such difference and the alternative hypothesis being that the endoscoping eye was poorer.

No global significant difference could be found between the endoscoping eye (E) and the other eye (N) for the urologists taken as a single group (tritan t=0.71; red/green t=0.78; P=n.s. on paired t tests). However, it was felt that differences in certain subgroups could be masked by a lack of difference in others, so the data were broken down into subgroups and reanalysed.

The total exposure time was estimated from information provided in the questionnaire in the following way: the number of hours allocated per week to carrying out endoscopy was multiplied by 40 (average number of weeks per year worked) and then by the number of years spent performing the procedure. A simple regression analysis was then performed to see if there was any relationship between the difference in threshold between the endoscope-using eye and the other eye (difference threshold = E − N) and the total exposure time. There was no significant relationship between the tritan difference and the total exposure time (t = −0.12, P=n.s. on 1-tailed analysis) (Fig. 1). A borderline significance was found between red/green threshold difference and total exposure time (t=1.56, P=0.06 on 1-tailed analysis) (Fig. 2).

The relationship between age and difference threshold was also examined; no significant relationship was found for either tritan gratings (t=0.25, P=n.s. on 1-tailed analysis) or red/green gratings (t=0.63, P=n.s. on 1-tailed analysis).

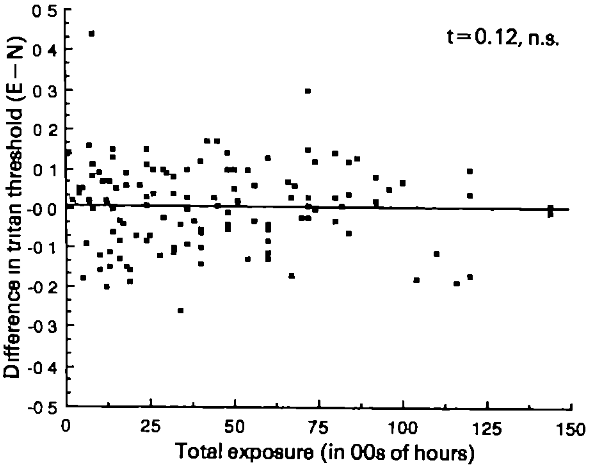

Fig. 1 Difference between tritan difference and total exposure time

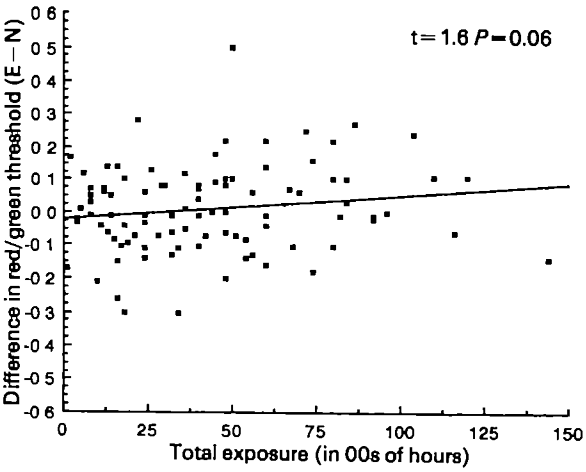

Fig. 2 Difference between red/green threshold and total exposure time.

Finally, subjects were placed into 1 of 3 age groups (31–40 years, 41–50 and 51+) and into 1 of 3 exposure time groups (0–4000 hours, 4000–8000, 8000+). A 2-way analysis of variance was then performed on the difference thresholds to ascertain the primary effects of age or exposure time, and secondary interactions between these 2 variables. No significant effects were seen for the tritan gratings but a borderline relationship was again observed between red/green difference thresholds and total exposure time (age $F = 0.52$, n.s.; exposure $F = 1.8$, $P = 0.8$; interaction $F = 0.29$, n.s.; 1-tailed test on 2-way ANOVA).

The difference in red/green threshold between the eye used for endoscopy and its fellow tended to increase with the total time exposed to endoscopy. This effect was of borderline significance on a 1-tailed comparison; it was not related to the subject's age and there was no evidence of an accompanying change in the tritan thresholds.

Discussion

The role of light absorption by the eye in the pathogenesis of various degenerative ocular conditions, such as cataract and age-related macular degeneration, is being increasingly recognised (Taylor *et al.*, 1988; West *et al.*, 1989). Excessive light exposure over short periods of time has been shown to cause specific macular changes both in experimental monkeys (Ts'o *et al.*, 1972) and in man (Robertson and Feldman, 1986). To date, a long-term modest increase in light exposure has not been shown to produce macular damage.

Several urologists described subjective differences of visual function between their 2 eyes; these consisted of differences in colour perception, differences in "focusing ability" and altered perception of light brightness. These complaints were further borne out by replies to the questionnaire.

It was our hypothesis that the surgeons might be suffering from macular damage as a result of the light exposure from the use of endoscopes and that this could be measurable with selective tests of macular function. A computer test of colour contrast sensitivity was used. This was specificially designed for the study to overcome the bias due to an awareness by the urologist of a subjective difference between the 2 eyes and leading to different thresholds for response for the 2 eyes.

Blue light is believed to be the most damaging part of the visible spectrum (Harwerth and Sperling, 1971) and a measure of blue light damage is indicated by the tritan threshold. The tritan threshold is thought to be specifically increased in early macular lesions. Whilst these results did not show a significant difference in tritan thresholds between the 2 eyes of the surgeons, there was a swing towards increased thresholds in the 41 to 50-year-old age group. Individuals in this particular group are likely to have had exposure to endoscopes (especially the higher powered light sources) from early in their surgical careers combined with relatively clearer ocular media and so have had relatively the longest exposures. The swing towards a higher threshold in the tritan axis in this age group suggests that the study could be worth pursuing.

The results clearly demonstrated the increase in tritan and red/green thresholds that is believed to occur with aging; this has long been suspected and presumed but not shown so clearly before.

Several inaccuracies became apparent during analysis of the data. It is difficult to estimate the hours spent endoscoping and a wide range of numbers was given. Whilst there may be large differences in the endoscoping hours, it was felt that some urologists recorded weekly theatre time rather than the number of hours actually spent looking down the endoscope. Thus the numbers of hours spent during a lifetime of surgery, as calculated, was probably inaccurate.

The test itself was difficult to explain, especially the concept that subjects had to respond even when they felt unable to see a stimulus at all. This problem was compounded for the non-English speaking urologists examined in Vienna. Their results may have been less reliable as a consequence.

The reflected light seen through endoscopes by the urologists is not particularly bright and so the result of using these lights would be unlikely to cause clinically significant changes. The present study was designed to detect very fine differences in macular functioning and not to detect overt pathology.

The opthalmic literature strongly suggests that blue light is the most damaging to the macula. The Department of Urology at the Whittington Hospital analysed the spectral emission of all instruments used by urologists to determine which were likely to be of greatest harmful potential as a result of high blue light content.

Whilst there was no marked significant difference in thresholds between the 2 eyes of the endoscopists, the borderline difference in red/green threshold and the trend towards the tritan axis differences suggest the possibility of very slight changes and it is hoped that there will be further opportunities to examine more subjects. The study may be extended to other groups of endoscope users in the future.

Power of the study

The power of the study was calculated; for the group as a whole, 3000 subjects would need to be examined for the results to achieve a significance level of 5% with an 85% acceptability level, for both the tritan and the red/green axes differences. However, for the group aged 41 to 50 years, where the trend towards a higher tritan threshold was found in the endoscoping eye, 300 subjects would need to be studied with respect to the tritan axis. The power for the red/green axis was much lower, requiring well over 3000 subjects alone in this age group to reach the same levels of significance and acceptability as above. There were 38 subjects in this age group in the present study.

There are many possible explanations for the subjective differences noticed between the 2 eyes by some individuals; this study has not shown macular damage of a degree sufficient to be detected by our means of testing.

We therefore conclude that, as indicated by our means of testing, too much urology does not damage the macula.

Acknowledgements

We thank all of the urologists who were so generous with their time in taking part in this study.

Many people have been very helpful, both in the offering of advice and in the organisational aspects. In particular, we would like to thank the following: Dr J. D Mollon, Department of Psychology, University of Cambridge; Mrs Pat Neville, Secretary of BAUS, Mr R C. L. Feneley and the Instrument Committee of BAUS; Professor M. Marberger, Vorstand der Urologischer Klinik der Universität Wien Mrs Jennifer Birch, City University, Department of Optometry

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Blue Light Emission from Urological Equipment. Can it Damage the Eyes?

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Summary—Blue light present in the visible spectrum at the lower wavelengths can cause damage to the retinas of monkeys and rats. In the present study the light sources and instrumentation available to the urologist were evaluated to see whether they posed a hazard. The light emitting directly from the sources, cables and telescopes was tested and these levels were found to be dangerous to the eye when compared with the safety limit recommended by the American Conference of Governmental Industrial Hygienists (ACGIH).

When the light at the eyepiece of the telescopes which had been reflected off a surface was measured, the blue light levels did not appear to be harmful when compared with the ACGIH safety limit.

The use of filters is discussed and the transmission of 2 types of filters shown.

While the level of blue light emission from the eyepiece remains within the ACGIH level, there are no data on long-term exposure. The addition of a blue light filter may be beneficial until such time as videoendoscopy becomes the norm. The light from light sources should be protected by a shutter and more care taken with the emission from cables and telescopes.

It is well known that several forms of radiomagnetic radiation can be harmful to living tissue, in particular the eyes and the skin. It has been shown that intense blue light causes photochemical damage to the retina of rhesus monkeys (Harwerth and Sperling, 1971) and rats (Van Norren and Schellekens, 1990). The radiant exposure required to produce a photochemical lesion is several orders of magnitude below that needed to produce a retinal burn (Ham *et al.*, 1978). The aim of this investigation was to see whether urological light sources produced blue light and, if so, whether it was of a sufficient level to damage the urologist's eyes.

Blue light (400–480 nm) is part of the visible spectrum of light (380–760 nm). When the sun is overhead and white, staring at it for 90 s will produce a blue light retinal injury (Sliney, 1986a). However, the natural aversion to bright light prevents one from staring at such bright sources. Previous experiments with rhesus monkeys have shown that blue light at 440 nm has the most damaging effect. The blue light radiance limit recommended by the American Conference of Governmental Industrial Hygienists (1990) is 100 W/m^2-sr for $t > 10{,}000$ s. Our results were compared with this figure. No data are available on continuous long-term low level exposure in humans.

Materials and Methods

Study 1

This study was divided into 3 parts. In the first part (study 1), 3 types of light source used in endoscopy—quartz halogen (150 W bulb), metal halide (400 W bulb) and a xenon light source (75 W bulb)—were tested. Although the xenon light source was not urological, it would have an identical emission spectrum. The xenon light sources available in urology have a 500 W bulb. We measured the emission spectrum from each type of light source to

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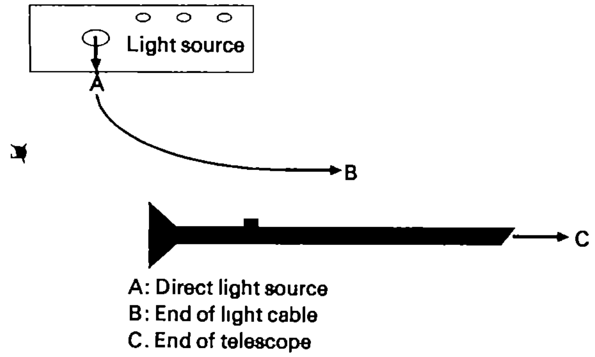

Fig. 1 Method of light analysis Study 1

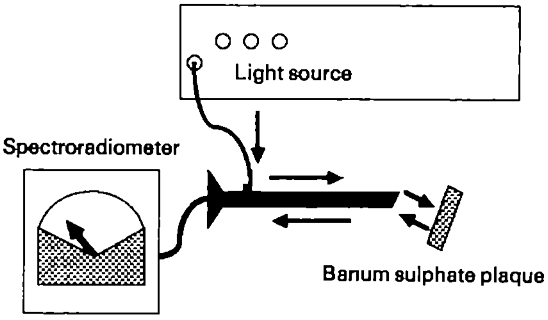

Fig. 2 Method of light analysis Study 2

establish whether they produced blue light and we then calculated the radiance of blue light from the light source directly. Secondly, the light at the end of the 2 different types of cable without telescopes and also the light coming from the end of the telescopes, again viewed directly (Fig. 1), were examined. None of these measurements represented the light to which the endoscopist would be exposed during a normal procedure.

Study 2

In urology and other specialties where endoscopes are used, one does not look directly at a light source but at light reflected from an illuminated surface. In this main study we measured the amount of light reaching the eyepiece of different sized and angled telescopes after the light was reflected off a surface. The reflective surface was a barium sulphate plaque, which is more reflective than would be expected from epithelial tissue in the body. The plaque was placed 5 cm from the end of the telescope. Each telescope was tested with 2 different light sources at maximum power (quartz halogen and metal halide) and with 2 types of light cable (liquid and fibre bundle). The amount of blue light given off by an electrohydraulic lithotriptor probe which had been passed down a nephroscope and placed in a basin of water was also measured. No reflecting surface was used in this test.

The measurements were performed using a photoradiometer. Although many different types of instrument were tested, the results were based on the telescope used most frequently in urology (4 mm telescope) and the telescope with the worst result (10 mm laparoscope). The experimental method can be seen in Figure 2. The spectral irradiance (300–800 nm) was measured, thereby including all visible light. From this the weighted irradiance of blue light was calculated (Sliney, 1986b) and divided by the solid angle to give the blue light radiance level. This was compared with the ACGIH (1990) hazard level of 100 W/m^2-sr ($t > 10{,}000$ s).

In the third study the ways of protecting the eyes from blue light were evaluated. Videoendoscopy is the safest method. A cheaper and more practical option would be a filter. The transmission of 2 types of filters (reflective and absorptive) is shown in Figure 3. It demonstrates how they can be effective at filtering out particular wavelengths of light.

Results

Study 1

In this initial study all 3 light sources emitted blue light as part of the spectrum (Figs 4, 5 and 6) and these radiance levels were well above the safety level proposed by the ACGIH (1990) when looking directly at the naked source. Similarly, the light shining out of the end of the cables and the telescopes, if viewed directly, was also above the safety level (Table 1).

Study 2

The light reflected off the barium sulphate plaque and measured at the eyepiece of the telescopes was well below the level proposed by the ACGIH (1990) in all instruments and with all light sources (Table 2). These measurements reflect the light level to which the endoscopist would be exposed during a procedure.

The amount of blue light given off by the electrohydraulic lithotriptor is minimal and has not been included in the results.

Study 3

Figure 3 shows the filter transmission of a reflective and an absorption filter. Each can take out a range

Table 1 Radiance Levels Directly from the End of the Cables and the End of the Telescopes

Telescope	*Quartz halogen*	*Metal halide*	*Fibre cable*	*Liquid cable*	*Radiance level (W/m²–sr)*
—	*		*		787
—	*			*	2000
—		*	*		2166
—		*		*	7143
Laparoscope 0°		*		*	6930
Laparoscope 0°		*	*		4042
Laparoscope 0°	*			*	1472
Laparoscope 0°	*		*		736
4 mm Urology 25°		*		*	5417
4 mm Urology 25°		*	*		3295
4 mm Urology 25°	*			*	902
4 mm Urology 25°	*		*		586

Table 2 Radiance Levels Measured at the Eyepiece of Various Telescopes

Telescope	*Quartz halogen*	*Metal halide*	*Fibre cable*	*Liquid cable*	*Radiance level (W/m²–sr)*
Laparoscope 0°		*		*	16.7
Laparoscope 0°		*	*		13 02
Laparoscope 0°	*		*		1 76
Laparoscope 0°	*			*	2.74
4 mm Urology 25°		*		*	1.62
4 mm Urology 25°		*	*		1 23
4 mm Urology 25°	*		*		0 16
4 mm Urology 25°	*			*	0.28
4 mm Urology 70°		*		*	0.68
4 mm Urology 70°		*	*		0.58
4 mm Urology 70°	*		*		0.09
4 mm Urology 70°	*			*	0 14

of light or a percentage of the light at particular wavelengths. Filters were tested clinically (mounted on the eyepiece) and it was found that the absorption filter (filter 2) took out too much blue light, impairing diagnostic ability. Filters which take out most blue light but leave some so that the image is not too yellow are currently being evaluated.

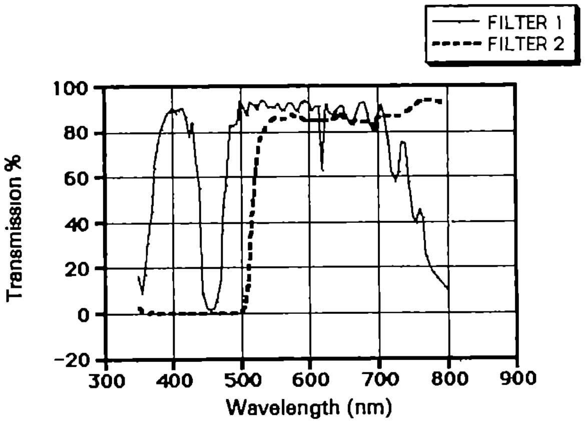

Fig. 3 Transmission of an absorption and reflective filter showing how certain parts of the spectrum can be filtered out.

Discussion

Animal experiments have shown the effect of looking directly at intense blue light. According to the results from study 1, if urologists were to look directly at either the light source or the light from the end of the cable and telescope, the levels of blue light would produce photochemical lesions on the retina. This emphasises the importance of caution when using these instruments in theatre. It is recommended that the light source be turned on only after it has been introduced into the access tract and that it be turned off before removal. Shutters fitted to light sources would prevent exposure if the light cable were to become detached from the source. This light hazard would affect not only the endoscopist but also other theatre staff.

The results also show that liquid cable transmits more light than the fibre cable. The light sources contained different powers of light bulb, so that the metal halide (400 W) produced more light than the quartz halogen lamp (150 W).

The amount of light reflected off the illuminated surface and transmitted to the eyepiece of the instrument (study 2) does not appear to be sufficient to cause blue light damage to the retina when using the ACGIH safety level of 100 W/m²-sr ($t > 10{,}000$ s). It should be noted that the radiance levels from the metal halide source are always considerably more than those from the quartz halogen source. The metal halide source is designed for videoendoscopy and should not be used in operator visual endoscopy.

The effects of low level chronic exposure are not known; whether long-term exposure may account for the changes in urologists' eyes needs further evaluation. As indicated by Ham *et al.* (1978), there is no assurance that long-term exposure to short wavelengths in the visible spectrum is harmless and protective filters are recommended for those who are chronically exposed to bright lights.

Filters fitted to instruments have been used to

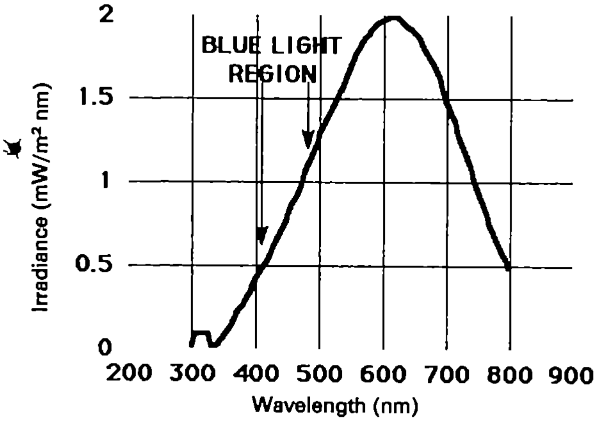

Fig. 4 Emission spectrum from a quartz halogen lamp (150W).

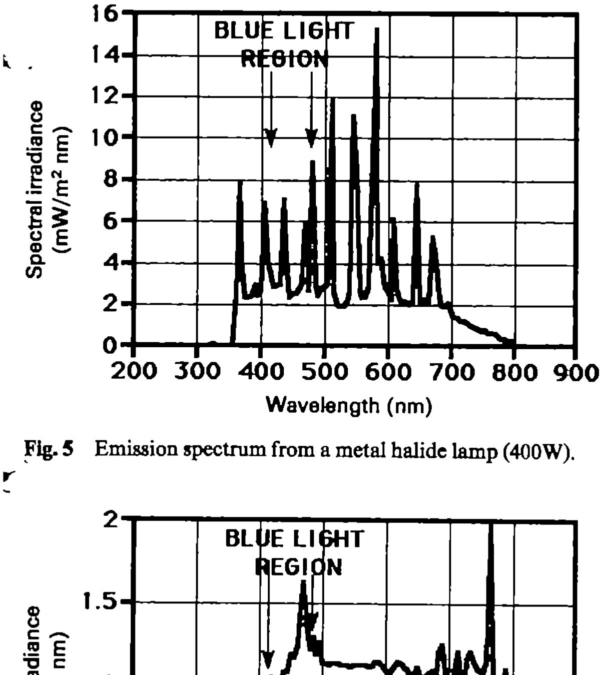

Fig. 5 Emission spectrum from a metal halide lamp (400W).

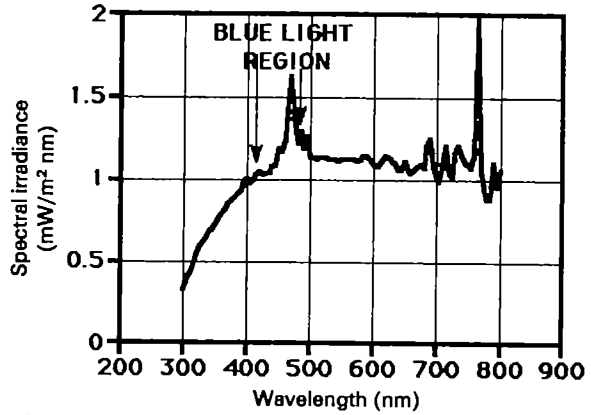

Fig. 6 Emission spectrum from a xenon lamp (75W)

protect the operator's eyes in indirect ophthalmoscopic photocoagulation (Whitacre *et al.*, 1990). Although it may be considered an over-reaction, a glass filter might be appropriate until it has been proved that long-term exposure to this level of light is totally harmless.

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Abdominal Aortic Aneurysms Presenting as Renal Colic

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Summary—In a 6-year period, 9 patients were referred by their General Practitioners to the urology unit with a clinical diagnosis of renal colic but were subsequently found to have leaking abdominal aortic aneurysms (AAA). In all cases of loin pain, especially in the elderly patient, the possibility of a leaking abdominal aneurysm must be considered. If no intrinsic urological cause for the pain is found or patterns suggestive of ureteric obstruction are seen on urography, ultrasound examination of the aorta-iliac vessels should be performed. Magnetic resonance imaging (MRI) and computed tomography (CT) scans may be useful adjuncts to this investigation.

Increased longevity and an increase in arterial disease has resulted in a rising incidence of abdominal aneurysms. The incidence of rupture is increasing, especially in women (Thomas and Stewart, 1988). Without surgery the overall mortality rate for ruptured abdominal aortic aneurysm (AAA) approaches 100% (Castleden *et al.*, 1985; Harris *et al.*, 1986). The high mortality rate following rupture is thought to depend more upon failure to operate than on peri-operative mortality (Johansson and Swedenborg, 1986). In those who are operated upon following rupture, mortality rates of 40–60% have been reported (Campbell *et al.*, 1986; Harris *et al.*, 1986) and these figures may be improved by treatment in a specialist centre (Jenkins *et al.*, 1986). In patients with an AAA, renal colic may result from (1) incidental intrinsic renal/ureteric obstruction, (2) ureteric compression secondary to aneurysm or aneurysm-associated retroperitoneal fibrosis or (3) aneurysmal dissection. The diagnosis of AAA may be significantly delayed by its presentation indicating referral to urological specialists. Consequent delay in making the diagnosis of an acute or dissecting AAA may delay treatment and adversely affect prognosis. The presentation of aneurysmal-derived loin pain may share many of the features of classical renal/ureteric colic and thus mislead the clinician. The case records of patients admitted to this unit with renal colic, who were subsequently found to have an aortic aneurysm accounting for their symptoms, have been reviewed. Imaging techniques are considered in an attempt to reduce morbidity and mortality.

Patients and Methods

Between 1984 and 1990, 9 patients presented to the urology wards with symptoms of loin pain attributable subsequently to an AAA. During any one year, an average of 75 patients were referred from General Practitioners with loin pain and a presumptive diagnosis of ureteric/renal colic. All 9 patients in the present series were male and the average age was 63.1 years (range 47–73).

Results

In 3 patients the diagnosis of ruptured AAA was obvious on admission and all subsequently died. A further 3 patients had urograms showing pelviureteric dilatation and in 1 patient an opacity suggestive of a stone was present (Table). Intravenous urography, retrograde ureterography and a nephrostogram delineated the site of ureteric obstruction. Ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) were required to show aortic dilatation. Figures 1 and 2 show the nephrostogram and coronal MRI appearances

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Table Details of Patients

Patient no.	*Age (years)*	*Side*	*Clinical features*	*Delay until diagnosis*	*Outcome*
1	68	L	Hypotensive on admission	—	Died on ward
2	47	L	1-month history of ejaculatory impotence, IVU/retrograde showed obstructed (L) kidney secondary to mid-ureteric compression	3 days	Successful elective repair
3	62	R	Stretched (R) ureter on IVU	14 h	Successful urgent repair
4	67	R	Plain abdominal film revealed calcified wall of AAA	6 h	Successful elective repair
5	61	L	IVU retrograde showed mid-ureteric obstruction	24 h	Successful elective repair
6	73	L	IVU/retrograde showed ureteric obstruction at pelvic brim	2 days	Elective successful graft for inflammatory AAA
7	61	L	Hypotensive with tender abdomen on admission	—	Died during attempted repair
8	59	L	Hypotensive with tender abdomen on admission	—	Died following attempted repair
9	70	L	No obvious cause for renal colic, sudden hypotension at 48 h	2 days	Died during attempted repair

obtained in patient no. 6 with an aorto-iliac aneurysm. In only 3 patients was a mass felt at initial presentation. Despite immediate assessment and intravenous urography the diagnosis was not immediately apparent in 6 patients.

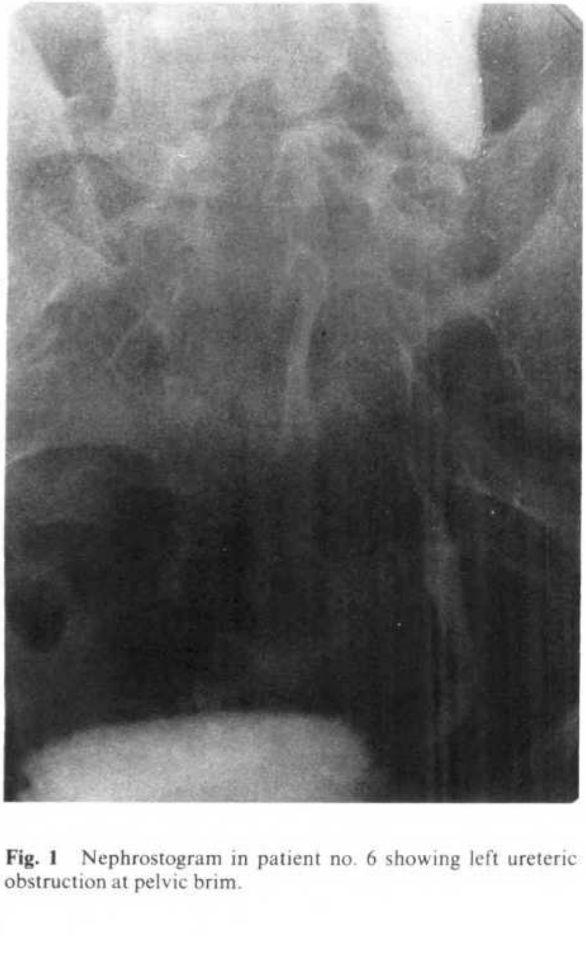

Fig. 1 Nephrostogram in patient no. 6 showing left ureteric obstruction at pelvic brim.

Discussion

The majority of patients with loin pain admitted to a urological ward will have a urinary tract stone or features strongly suggestive of the passage of a calculus. However, a proportion of patients will

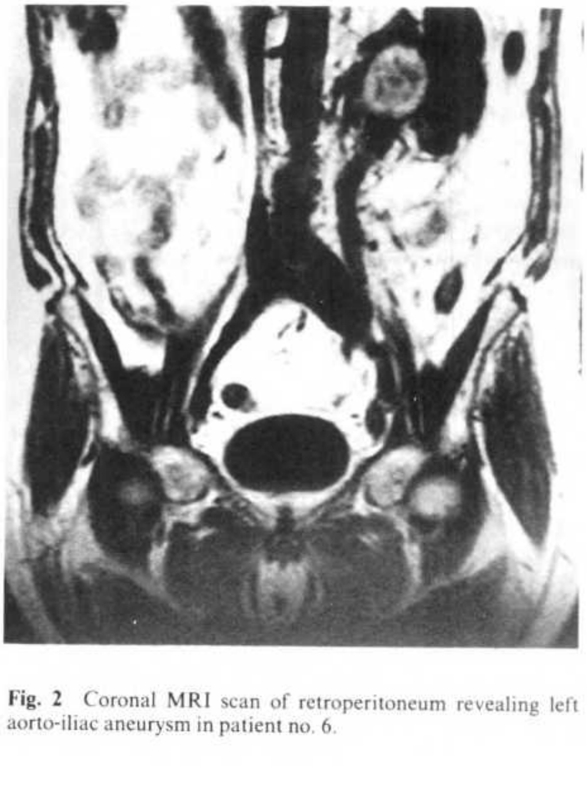

Fig. 2 Coronal MRI scan of retroperitoneum revealing left aorto-iliac aneurysm in patient no. 6.

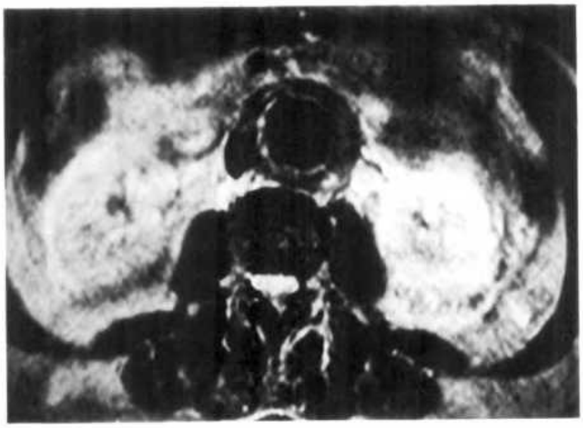

Fig. 3 L2 transverse section through inflammatory AAA in patient no. 3.

have other conditions, including intestinal, gynaecological, retroperitoneal and spinal pathology. The proximity of the ureters to the aorta, especially on the left, makes them particularly liable to be involved in aortic pathology. It is important not to overlook potentially lethal conditions such as AAA when confronted with a patient with renal colic. In particular, the presence of hypotension or an abdominal mass should arouse suspicion. A high level of suspicion should be maintained particularly in cases of renal colic in the elderly. Inflammatory AAAs (Fig. 3), however, tend to occur in a younger age group than atherosclerotic aneurysms. In this group there is a higher incidence of symptoms associated with the intact inflammatory aneurysm and rupture is less common (Walker *et al.*, 1972). As with non-inflammatory AAAs, loin pain may signal stretching of the aneurysmal sac and incipient rupture. The establishment of regional vascular surgery units over the last 2 decades has resulted in an increasing survival rate for those patients with ruptured abdominal aneurysms (Jenkins *et al.*, 1986). Early referral to these units from urology units may improve the prognosis for this group of patients. Although only 9 symptomatic aneurysms were found in approximately 450 patients admitted with loin pain over a 6-year period, a high level of awareness of this condition should exist among urological resident staff.

The investigation of a patient with renal colic should include an urgent intravenous urogram and an ultrasound examination of the kidneys. The degree of urgency of such investigations is a matter of debate and in many units they are often performed during the next working day. There is a strong argument for immediate radiological assessment both to exclude other pathology and to make a diagnosis—in order to initiate treatment or discharge the patient. This service may be offered either by the relevant department of radiology or by urologists trained in basic imaging techniques. Where clinical or radiological suspicion of an abdominal aneurysm exists, additional more specialised techniques may be of value. MRI produces images in 3 planes (axial, coronal and sagittal) and can give a detailed assessment of the retroperitoneum. If available, it may be the investigation of choice for the assessment of potential retroperitoneal pathology.

In any patient presenting with loin pain, especially those over the age of 50 years, a detailed history and full examination should be performed. Symptoms of peripheral vascular ischaemia and the presence of an abdominal mass or hypotension should add further urgency to the investigation.

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Psychological Aspects of Female Urinary Incontinence in General Practice

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Summary—The aim of this study was to determine whether urge incontinence was associated with a higher prevalence of psychological symptoms than other types of incontinence. The psychological aspects of 110 women presenting with urinary incontinence in general practice were assessed by means of standardised questionnaires and medical history-taking. The results showed no difference in psychological characteristics between patients with urge incontinence and those with other types of incontinence. These findings were contrary to the conclusions of almost all other studies based on populations selected for specialist care.

It was concluded that in general practice the psychological approach to urinary incontinence depends more on the individual needs of the patient than specifically on the type of incontinence.

Urinary incontinence is a common problem in women aged 20 to 65 years (Thomas *et al.*, 1980; Holst and Wilson, 1988; Lagro-Janssen *et al.*, 1990). Genuine stress incontinence accounts for most cases in general practice, followed by urge incontinence and mixed incontinence (Jolleys, 1988; Lagro-Janssen *et al.*, 1991). Neurological causes are rare.

In patients with urge incontinence the (muscular) sphincter systems are usually intact but inhibited detrusor contractions lead to incontinence.

Psychiatric and psychological factors are said to be important in the aetiology of urge incontinence. Frewen (1978, 1984) in particular implicated psychological factors. Others have reported high levels of neuroticism (Freeman *et al.*, 1985), depressive and anxiety disorders (Ferrie *et al.*, 1984; Macaulay *et al.*, 1987) and a tendency to somatisation (Dijkstra *et al.*, 1987). Urge incontinence is usually considered to be psychosomatic.

All studies, however, consisted of patients referred for specialist treatment and few studies have included control groups of women with other types of urinary incontinence. If psychological factors are of aetiological significance, it might be expected that patients with urge incontinence will demonstrate a higher level of emotional disturbance than patients with other types; in addition, all patients, and not only a selected group, will demonstrate this disturbance. We have therefore studied this phenomenon in a less selected population (patients presenting with urinary incontinence to their general practitioners (GPs) in order to determine whether urge incontinence was associated with a higher prevalence of psychological symptoms than other categories of incontinence.

Patients and Methods

Between January 1987 and January 1990, 13 GPs selected female patients (age range 20–65 years) who had complained of urinary incontinence. Excluded were women with a previous operation for incontinence, an underlying neurological cause for incontinence (e.g. diabetes mellitus) and urinary tract infection. Microscopy and, if necessary, a urine culture were carried out in order to exclude urinary tract infection. All patients were examined by the same GP (A.L.M. L.-J.). A medical history and psychometric tests were taken, followed by a physical examination. The sociodemographic background was noted (age, marital status, parity,

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education). All patients underwent a complete urodynamic evaluation (including static and dynamic urethral pressure profiles, cystometry and uroflowmetry) and were diagnosed according to the criteria of the International Continence Society. The psychological assessment took place before the clinical evaluation; this ensured ignorance of the urodynamic diagnosis.

Urinary incontinence was defined as the involuntary loss of urine more than twice a month. The onset of the incontinence, its duration and severity were recorded. Severity was divided into 3 categories according to the frequency of urine loss and the use of protective pads or garments: mild (3–4 times a month or a few times a week but requiring no protective pads); moderate (a few times a week or daily but requiring protective pads only occasionally or not at all); severe (daily and requiring protective pads most of the time) (Thomas *et al.*, 1980). Duration was also divided into 3 categories; up to 2 years, 2 to 5 years and more than 5 years.

The patient's mental state was assessed according to:

(1) The presence of mental disorder, including emotional and anxiety disorders, classified on the basis of the E-list, a classification in primary care derived from the International Classification of Disease (van den Hoogen *et al.*, 1985).
(2) The use of psychotropic drugs such as tranquillisers and hypnotics.

The following standardised questionnaires were used:

(1) The Health Locus of Control Internal and External (Wallston and Wallston, 1981), which measures the extent to which people perceive responsibility for their health. A high score on the internal orientation indicates a low perception of self-responsibility, while a high score on the external orientation indicates a high perception of self-responsibility (rating scale 1–5).
(2) A functional somatic complaint scale—the VOEG (Dirken, 1969), which measures somatic and functional complaints due to stress. A high score indicates a high level of perceived stress (range 0–21).
(3) A scale measuring anxiety (van der Ploeg *et al.*, 1980). The lower the score the less the degree of anxiety (range 1–7).
(4) A scale measuring perceived physical and mental health status by asking the patient how she would classify her own condition (excellent, good, reasonable, poor, bad). The lower the score, the better the physical or mental condition (range 1–5).

Statistical analysis was based on χ^2 and Student's *t* tests. The study was approved by the Medical Ethics Committee of the University of Nijmegen and the women gave informed consent.

Results

Thirteen GPs selected 146 women with urinary incontinence; 36 refused to participate, however, mainly because they did not consider their urinary incontinence serious enough to undergo further investigation (response rate 75%). There were no differences in sociodemographic data or the type of incontinence between participants and non-participants. Mild incontinence was confirmed as more frequent among the non-participants (Table 1).

The study group thus consisted of 110 women; 66 (60%) had genuine stress incontinence, 20 (18%)

Table 1 Details of Patients (in percentages)

	Participants (n=110)	*Non-participants (n=36)*	P/χ^2
Age (years)			
20–34	18	22	
35–44	39	42	ns
45–65	43	36	
Parity			
0	12	14	
1–3	75	75	ns
>3	13	11	
Marital status			
Married	86	89	
Single	6	3	ns
Widowed/ divorced	8	8	
Education			
Low	53	53	
Middle	31	25	ns
High	17	22	
Type of incontinence			
Stress	60	67	
Urge	16	11	ns
Mixed	18	19	
Other	6	3	
Severity			
Mild	7	56	
Moderate	57	28	
Severe	36	11	$P<0.01$
Unknown	–	5	

ns = not significant

had mixed incontinence and 18 (16%) had urge incontinence (including detrusor instability and sensory incontinence). Six patients had no demonstrable incontinence on urodynamic tests. Most patients were aged between 35 and 54 years. Table 2 summarises the results. Patients with genuine stress incontinence were significantly older than those with urge incontinence. No other significant differences were found. Patients with urge incontinence had no more nervous and psychiatric disorders and used no more psychotropic drugs than other incontinent patients.

The psychological factors measured did not distinguish between urge incontinence, genuine stress incontinence and mixed incontinence.

Discussion

Since the study by Frewen (1978), most reports have highlighted the association between urge incontinence and psychological symptoms. Some authors suggested that the urinary symptoms were causally related to the abnormal mental state (Frewen, 1984; Macauley *et al*, 1991) but Norton *et al.* (1990) reached a different conclusion. They investigated 105 women attending an out-patient urodynamic clinic and reported that detrusor instability was not associated with a higher prevalence of psychiatric morbidity than was found in other incontinent patients.

Our results do not implicate psychological factors in the aetiology of urge incontinence. On the contrary, we found no striking differences between the 3 groups. There are several possible explanations for the difference in results between the various studies.

Firstly, most studies are based on patients referred for specialist treatment or patients who accept an invitation to participate in a study on urinary incontinence. It is known that patients' psychosocial problems influence the decision to refer them for specialist care (Lamberts, 1984). Thus one can expect more psychological symptoms in a referred population.

Secondly, most studies lack a control group of other incontinent patients and compare their scores

Table 2 Details of 110 Women and Type of Incontinence

	Urge incontinence (n=18)	*Mixed incontinence (n=20)*	*Genuine stress incontinence (n=66)*	*No incontinence (n=6)*	
Mean age (std)	37.4 (10.6)	45.2 (9.2)	45.3 (10.2)	34.8 (11.1)	x
Mean parity (std)	1.7 (1.5)	2.8 (1.3)	2.3 (1.3)	1.7 (2.1)	ns
Onset related to pregnancy or delivery (no.) (%)	3 (17)	6 (30)	27 (41)	2 (33)	ns
Duration of incontinence (no.) (%)					
<2 years	12 (67)	6 (30)	18 (27)	3 (50)	ns
2–5 years	4 (22)	5 (25)	19 (29)	1 (17)	
>5 years	2 (11)	9 (45)	29 (44)	2 (33)	
Severity of incontinence (no.) (%)					
Mild	0 (0)	1 (5)	6 (9)	0 (0)	ns
Moderate	10 (56)	9 (45)	37 (56)	5 (83)	
Severe	8 (44)	10 (50)	23 (35)	1 (17)	
Presence of nervous and psychiatric disorders (no.) (%)	5 (28)	6 (30)	7 (11)	1 (17)	ns
Use of psychotropic drugs (no.) (%)	2 (11)	0 (0)	5 (8)	0 (100)	ns
Mean score (std)					
Health Locus Control Int.	2.83 (0.34)	2.92 (0.32)	2.91 (0.16)	3.15 (0.56)	ns
Health Locus Control Ext.	3.04 (0.40)	2.63 (0.36)	2.83 (0.18)	3.35 (0.66)	
Anxiety Rating Scale	2.06 (0.26)	1.96 (0.26)	2.06 (0.12)	2.19 (0.44)	
VOEG (General Health Questionnaire)	9.59 (2.70)	7.58 (2.52)	6.72 (1.26)	7.60 (4.58)	
Perceived physical health	2.28 (0.44)	2.45 (0.42)	1.97 (0.20)	2.17 (0.70)	ns
Perceived mental health	2.11 (0.38)	1.75 (0.36)	1.97 (0.16)	1.83 (0.60)	

x = *t* test $P < 0.01$.
ns = not significant.

with those of a normal population. These 2 factors stress the importance of including a control group and the need to be aware that selection of patients can influence the results. Our findings contradict the assumption that patients with urge incontinence differ psychologically from patients with other types of incontinence. We believe this reflects our methodology, which incorporated control groups and defined diagnostic entities.

This study has produced a negative result, *i.e.* it failed to confirm an assumed correlation based on previous studies. Nevertheless, this negative result is probably of practical relevance: urinary incontinence has obvious implications regarding the patient's life (Lagro-Janssen *et al.*, 1990; Hunskaar and Vinsnes, 1991; Vinsnes and Hunskaar, 1991). It is an embarrassing and occasionally frightening complaint where patients have to cope as best as they can. The general practitioner must take into account these individual consequences in order to provide adequate care. In this respect the type of incontinence is of little value.

The hallmark of adequate care in urinary incontinence is effective treatment. There is growing evidence of the effectiveness of simple treatment in general practice (Jolleys, 1989). Here, the type of incontinence should be taken into account. Bladder training appears effective in the treatment of detrusor instability, whereas pelvic floor exercises are the first choice in stress incontinence. However, the present study casts doubt on the specific psychosomatic aetiology of detrusor instability. As a consequence, in general practice the psychological approach to urinary incontinence should be the same in all types of incontinence and should focus on the needs of the individual patient.

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Epidural Anaesthesia in the Management of the Painful Bladder

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Summary—Bladder pain is a difficult symptom to manage. Epidural anaesthesia, which was used in 10 patients with sensory disorders, carries a low morbidity and helps to define those patients with severe bladder pain who might benefit from denervation procedures.

Sensory disorders of the bladder are difficult both to define and to manage. Bladder pain, as a dominant symptom in interstitial cystitis, or sensory urgency in the absence of intravesical pathology, are 2 areas where the disturbance of sensation from the bladder may be sufficiently serious to merit bladder denervation procedures (Worth and Turner-Warwick, 1973). However, cystolysis and cystocystoplasty are not procedures which should be undertaken lightly and it is important to define that group of patients whose sensory disorders are most likely to benefit from denervation. In particular it is important to exclude from surgery those patients with psychogenic problems referred to their bladder. We have used epidural anaesthesia in 10 patients with sensory disorders and report the experience.

Patients and Methods

A total of 10 women of mean age 42.7 years (range 25–52) underwent epidural anaesthesia as part of the investigation of sensory disorders. All had stable bladders on video-urodynamic testing. In all, 6 of the 10 had histologically proven interstitial cystitis with biopsy features fulfilling established diagnostic criteria. All had had previous cystoscopies with biopsy and all had a bladder capacity under anaesthesia > 300 ml. Frequency was the dominant symptom in 6 patients and suprapubic pain was dominant in 4, although all of the patients had significant pain amongst their symptoms. In some cases the pain gave features more suggestive of a urethral origin. Of these, 1 patient had severe frequency following a colposuspension and another had residual features of interstitial cystitis in the trigone following a caecocystoplasty 4 years earlier. The details are summarised in the Table.

Patients were admitted for epidural anaesthesia, for which an epidural catheter was inserted during the course of general anaesthesia for endoscopic examination. A wide epidural spread of local anaesthetic is needed to achieve afferent blockade from the level of the sacrum to the 10th thoracic sensory level and therefore a mid-lumbar approach (L2/3 or L3/4) was used. A Tuohy needle was inserted and an epidural catheter passed. The epidural was effected after general anaesthesia was concluded, with $\leqslant 25$ ml of 0.375% bupivicaine. The skin sensation was subsequently tested to ensure adequate spread of the anaesthetic agent and the patient's posture altered to achieve the required direction of flow. Ringer's lactate solution was infused intravenously whilst the block became established and thereafter a slow infusion of crystalloid was maintained to ensure adequate diuresis (1000 ml/12 h until the morning after the procedure). There were no restrictions on dietary or fluid intake.

As far as possible, frequency volume charts were kept for 24 h before and 24 h after the epidural anaesthetic was instilled. Patients were confined to bed for 6 h following the procedure but were

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allowed to mobilise after this period. Patients were asked to document the relief, or otherwise, of their pain.

Results

No patient went into urinary retention and there were no complications attributable to the insertion of epidural anaesthetic. All patients have been followed up in the out-patient clinic for a minimum period of 12 months since the epidural anaesthetic was administered.

At follow-up, 3 patients reported no change in the pain perceived with epidural anaesthesia functioning. These include a mother and daughter whose symptoms are now considered to be psychogenic in origin. The third patient had symptoms which were thought to be largely due to urethral hypersensitivity, although she derived no relief with the epidural anaesthetic. Peri-urethral Marcain and hydrocortisone were administered, again without benefit.

Overall there was improvement in both the frequency of micturition experienced and the volume of urine voided. The mean pre-epidural void was increased from 116 ml (range 50–200) to 350 ml (50–500). The average interval between voids rose from 53 min (20–110) to 231 min (20–640). Nine patients experienced an increase in the voided volume and a decrease in the frequency of micturition. One patient had frequency, urgency and suprapubic pain following a colposuspension. Her frequency and voided volume were not affected by the epidural and she subsequently underwent a bladder neck reconstruction with a good functional result.

Therefore, 6 patients experienced improvement in both suprapubic pain and frequency of micturition. One of these patients was considered to have dominant urethral symptoms but has made a very poor response to all attempts at topical or local analgesia and denervation is being reconsidered. The other 5 patients were advised to undergo denervation procedures on the basis of their symptoms and their response to the epidural. All underwent cystolysis using the later modification of the technique (Worth, 1980). One patient had persistent pain and underwent cystocystoplasty before her symptoms improved. She is currently pain-free 2 years after surgery. Another 2 patients appear to have lost their pain following the surgery (both with follow-up greater than 2 years) and a further 2 are beginning to get recurrent symptoms 12 and 18 months after surgery.

Discussion

Bladder sensation arises from non-specific nerve endings in the lamina propria and submucosa. From this nerve plexus stimuli pass through nerve bundles within the detrusor muscle to the pelvic nerves and then via the 3rd and 4th sacral dorsal root ganglia to the spino-thalamic tract. Pressure and volume sensation also follow this pathway as

Table Details of Patients

			Results before/during the epidural				
Age (years)	*Histology*	*Dominant symptoms*	*Void (ml)*	*Frequency (min)*	*Pain relief*	*Management/surgery*	*Outcome/comment*
37	IC	Pain, frequency	200/500	60/210	Yes	Cystocystoplasty	Pain-free, failed cystolysis
52	IC	Frequency, pain	150/400	60/180	Yes	Cystolysis	Frequency, initial pain relief
40	IC	Frequency, urethralgia	130/300	40/150	Yes	Local analgesia	Partial relief only
32	Normal	Frequency, urgency	85/400	30/640	No	Local analgesia	No benefit
49	Normal*	Frequency, urgency	50/50	20/20	Yes	Bladder neck reconstruction	Frequency 2-hourly
47	IC	Frequency, pain	50/600	45/420	Yes	Cystolysis	Pain-free
43	IC†	Frequency, pain	160/200	90/120	Yes	Cystolysis	Pain-free
51	IC	Pain, urgency	50/300	15/150	Yes	Cystolysis	Frequency, initial pain relief
51	Normal	Pain, frequency	140/350	60/180	No	Local analgesia	No benefit
25	Normal	Pain, frequency	150/350	110/240	No	Nil	Psychiatric review

IC = interstitial cystitis. * Post-colposuspension † Previous caecocystoplasty.

the afferent limb of the micturition reflex (George and Dixon, 1986). The preservation of these sensations during the course of the epidural is related to fibre size. The hypogastric nerve may also play a role in the transmission of pain but its division does not appear to relieve bladder pain completely. Also, our own experience suggests that it is necessary to block up to the T10 level to remove all afferent sensation from a distended bladder.

The rationale behind bladder denervation procedures and the success achieved at this hospital have been described (Worth and Turner-Warwick, 1973). Although the latter claimed that cystolysis was a relatively simple procedure for patients with bladder pain, there is a definite morbidity due to ischaemic bladder contracture which it is hoped is abolished by the preservation of at least 1 supravesical pedicle. Since 1973 we have seen a patient with Munchausen's syndrome on whom cytolysis has been performed with, not surprisingly, no therapeutic benefit. This experience and the difficulties in obtaining objective evidence from patients with sensory bladder disorders has prompted the use of epidural anaesthesia as a "reversible cystolysis". Other authors have suggested that the operation has a very poor success rate (Albers and Geyer, 1988), and whilst we accept that there will be a significant number of patients in whom the pain will return it is undoubtedly successful in some patients with very distressing symptoms. The preservation of 1 superior vesical pedicle avoids the complication of ischaemic bladder contracture and the operation of cystolysis should be offered if appropriate. It is suggested that the exclusion of some patients by preliminary assessment with epidural anaesthesia would improve the proportion of patients deriving lasting benefit.

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Does Residual Urine Predispose to Urinary Tract Infection?

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Summary—The relationship between the presence of post-micturition residual urine and urinary tract infection is unclear. We have performed a retrospective analysis of 342 studies on bladder emptying and compared the incidence of bacterial infection and pyuria in patients with residual urinary volumes of more or less than 100 ml. In patients with a residual volume > 100 ml 49/219 studies showed evidence of pyuria and 28/198 studies of patients whose residual urine was less than 100 ml showed evidence of infection. In cases where the residuals were > 100 ml 33/123 had evidence of pyuria and 19/109 infection. There was no significant increase in the rate of infection in patients with large residual urinary volumes, suggesting that there is no definite correlation between post-micturition residues and urinary tract infection.

In the absence of instrumentation or trauma, infections in the genitourinary tract can arise only from blood-borne organisms or organisms ascending from the external urethral meatus. The principal local defence mechanisms against infection are the antibacterial properties of the urothelial mucosa (Harrison *et al.*, 1988). It is also widely assumed that the irrigating effect of free-flowing urine (Pollock, 1987) and the absence of urinary stasis (Mathews *et al.*, 1982) contribute to averting urinary tract infection. Whilst this would seem to be the case in children (Hansson *et al.*, 1990), ileocystoplasties (George *et al.*, 1991), diabetics (Kitami, 1991) and patients with multiple sclerosis (Kornhuber and Schutz, 1990), there is little evidence about the exact relationship between the presence of residual urine in the bladder and urinary tract infection in the adult population.

In an attempt to clarify this issue we performed a retrospective analysis of the records of 318 patients undergoing assessment of bladder emptying by ultrasound cystodynagram (USCD) or videocystometrogram (VCMG) and identified those patients with infected urine based on standard criteria.

Patients and Methods

The patients were identified from the records of the X-ray department and include all USCDs performed during a 12-month period. Also included were 74 patients whose bladder emptying was studied by VCMG and for whom microbiological data were available. The presence or otherwise of urinary tract infection corresponding to these emptying studies was determined from midstream urine (MSU) specimens provided within a 4-week period prior to the USCD or VCMG.

The technique of USCD has been described previously (Boothroyd *et al.*, 1989). The residual volume was calculated using the formula height × breadth × depth × 0.7 (Poston *et al.*, 1983). In this study we did not concern ourselves either with uroflowmetry or the indications for investigating the underlying voiding dysfunction. There is well recognised variability in residual volume and for the purposes of this study a significant volume was considered to be greater than 100 ml.

MSU results were analysed for the presence of white blood cells (WBC) or bacteria in the urine.

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Information on the numbers of WBC in the urine was recorded in 3 groups: group 1—those with less than 20 WBC/hpf; group 2—those with 20–100 WBC/hpf; group 3—those with >100 WBC/hpf. Bacterial infection was considered established if there were more than 10^7 organisms/l. Mixed bacterial growths were noted, as were specific organisms. Comparisons on the incidence of infected urine and pyuria in studies with and without urinary residuals were made using the χ^2 test.

Results

In all, 290 USCDs were performed in the 12-month period; 22 of these were excluded because MSU results could not be traced. The remaining studies were carried out on 244 patients; 20 patients had 2 investigations and 2 were studied 3 times. Also included in the analysis were 74 patients whose MSUs were taken for a study on antibiotic prophylaxis in VCMG. This gave a total of 342 studies on bladder emptying for which corresponding microbiological data were available.

The records of 318 patients (239 men and 79 women) were studied. Their mean age was 61 years (range 23–89), with the men being older than the women (mean age 65 *vs* 52 years). The following analysis relates to investigations rather than patients, although results were analysed with regard to the latter as well. The results are summarised in Table 1.

Nineteen MSU speciments showed group 2 pyuria, of which 10 demonstrated bacterial growth; 63 showed group 3 pyuria, of which 47 had bacterial growth. *Escherichia coli* was cultured in 28 cases, mixed growth in 9, and 25 specimens grew assorted single organisms.

A total of 123 studies (36%) showed residual urine >100 ml (100 male, 23 female). Seven of these had group 2 pyuria, of whom 3 had definite bacterial growth, and 26 had group 3 pyuria, of whom 19 had bacterial growth. Of 219 studies showing residual volumes <100 ml, 12 had group 2 pyuria and 37 had group 3 pyuria; bacterial growth was obtained from 7 and 28 MSUs respectively. Thus 33/123 studies with residuals >100 ml had microbiological results suggestive of infection (male 26/100, female 7/23) and 49/219 studies with residuals <100 ml suggested infection (28/155 male, 21/64 female). The results are detailed in Table 2.

In 47 studies definite urinary tract infection was defined by bacterial growth and WBC >100/hpf; 19 of these had residuals >100 ml. If patients with group 2 or 3 pyuria without bacterial growth and those with group 2 pyuria and growth were excluded, 28/198 patients with residuals <100 ml and 19/109 with residuals >100 ml had definite infection. No pairing male or female, definite infection or suggested infection (pyuria), showed any significant difference for the presence or otherwise of residual urine.

Twenty-two patients were studied more than once; 8 of these had studies which showed no evidence of infection and left residuals of >100 ml on one study and <100 ml on the other. Ten of these 22 had evidence of infection on at least one study, of whom 4 had residuals <100 ml, 3 had residuals >100 ml and 3 had both results on occasion. In the latter group infection was present with the smaller residuals measured. Twenty patients left residuals of more than 400 ml; of these, 4 (20%) had definite evidence of infection and 17 patients voided more than 800 ml, of whom 4 (22%) had infections.

Table 1 Number of Voiding Studies Demonstrating Pyuria and Bacterial Growth

	20–100 WBC/HPF No growth		*20–100 WBC/HPF + growth*		*>100 WBC/HPF No growth*		*>100 WBC/HPF + growth*	
Sex	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
Residual urine <100 ml (n=219)	4	1	2	5	8	1	14	14
Residual urine >100 ml (n=123)	4	0	2	1	5	2	15	4
Overall	8	1	4	6	13	3	29	18
Male and female	9		10		16		47	

Table 2 Number of Voiding Studies in Patients with Definite Bacterial Growth or Pyuria Suggestive of Infection

	Residual urine < 100 ml (%)	*Residual urine > 100 ml (%)*	χ^2
Definite bacterial infection			
Overall	28/198 (14.1)	19/109 (17.4)	0.55
Males	14/141 (9.9)	15/85 (17.6)	2.17
Females	14/57 (24.6)	4/20 (20.0)	0.53
Pyuria in groups 2 or 3 with or without bacterial growth			
Overall	49/219 (22.4)	33/123 (26.8)	0.63
Males	28/155 (18.1)	26/100 (26.0)	1.84
Females	21/64 (32.8)	7/23 (30.4)	0.00

None of the differences in the various pairings achieved statistical significance. χ^2 must be >3.84 for $P<0.05$.

Discussion

There should be no residual urine after micturition and it is tempting to speculate that residual urine acts as a culture medium. There is some evidence that this occurs in patients with neurological disease (Kornhuber and Schutz, 1990) and in patients with diabetes (Kitami, 1991). The results of the present study suggest that there is no predisposition to infection in patients with urinary residuals in the general adult urological population.

Measurements of urinary residual volumes are influenced by the interval between the void and the measurement, the presence of reflux or diverticulum and the state of hydration of the patient. In addition, the voided volume varies significantly for individuals between different voids (Birch *et al.*, 1988), and this experience is endorsed by our results from patients having more than one investigation. Furthermore, residual urine measurements differ with different methods of measurement. Despite these reservations, we feel that the use of a cut-off level as high as 100 ml for defining a significant residual will identify the majority of patients with significant incomplete voiding.

These results suggest that the presence of residual urine *per se* does not influence the incidence of urinary tract infection. Prospective studies are indicated to determine the role of instrumentation in causing infection in patients with significant residual volumes.

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and charity. He was a man of integrity and great benevolence, for he melted down his gold sounds and distributed the proceeds among the poor, but shortly after his death his name, inexplicably, was erased from the Parish register (Moloney, 1958).

Practice developed the skill of these lithotomists and by the early eighteenth century, the urethra and its prostatic parts could be opened with gentleness and it seldom took more than a minute to extract the stone. The operation was always considered to be the test of a real surgeon, for, in order to reduce the terrible pain, time had to be cut as severely as the patient. The surgeon needed, as well as a steady hand, a firm jaw and good teeth, for it was customary to hold the knife between the teeth so that the hands would both be free for essential manoeuvres. This ancient custom is now, fortunately, extinct.

The greatest of all lithotomists was Cheselden, who flourished some 70 years after Pepys. He set a record of 24 seconds to remove a stone. Of 213 operations only 20 patients died, a mortality rate of 9.3%—a remarkable record (Cheselden, 1723).

Pepys chose as his surgeon Thomas Hollyer, lithotomist and surgeon to St Thomas's Hospital, whose merit was later recognised by being elected Master of the Barbers' Company—an honour comparable today with the Presidency of the Royal College of Surgeons. He had a good reputation, cutting 40 patients in one year, all of whom survived. It was fortunate for Mr Pepys, as well as subsequent generations who read his diary, that Pepys was operated upon when he was, because subsequently Hollyer lost 4 patients, presumably because by this time his instruments had become septic (Power, 1931).

So, 5 years after the onset of his first symptoms at the age of 25, Pepys settled the day and the place of his ordeal. He chose the house in Fleet Street of a friendly fourth cousin, Mrs Turner—only wealthy people could afford to go into hospital—and Pepys was not yet a wealthy man. The day was 26 March 1658. Pepys did well to place his ordeal away from his own house to spare his young wife the sight and sound of his agony. His relatives and friends were all present, offering support and prayers.

He had 3 days' preparation, with purging, bleeding and fomentations to the peritoneum. His pre-medication, apparently effective, was opiate and mandragora, which was soaked into a sponge and given to the patient to inhale (Riches, 1977).

Following the arrival of the surgeon, his assistants and his bag containing the apparatus major, Pepys was laid on his back on a table in the lithotomy position, secured with ropes, arms pinioned, and held by 3 assistants. The surgeon, with catheter in his button-hole and the knife in his teeth, approached the patient. Pepys was doubtless transfixed with fear.

The operation was a lateral lithotomy, a modification introduced by Jacques which was a simpler and safer technique, replacing the brutal Marian operation (Riches, 1935). The presence of a stone would have been confirmed by bimanual examination and the passing of a metal implement along the urethra to sound the stone. An incision was made in the left side, medial to the ischial tuberosity on to the sound. The prostate and bladder neck were divided and a finger introduced, following by dilators and then forceps. We have the surgeon's word for it that "he had a very great stone taken that day from him". It was about as large as a tennis ball (Evelyn, 1952)—the size of a modern squash ball; it weighed 2 ounces and it was either a uric acid calculus or it had a uric acid nucleus with a covering of ammonium urate (Power, 1933).

After the operation Pepys was given 2 prescriptions, both of which are still in existence. The first, described by Dr Molleynes, Hollyer's old master, consisted of 6 ingredients, namely licquorice, marshmallow, cinnamon, milk, rose water and the white of eggs—none of which would do him the least good; the second was by Dr Joiliffe, the young physician, discoverer of the lymphatics, and consisted of lemon juice and syrup of radish which, of course, would do him no harm. He was evidently in safe hands.

It is also clear that his surgeon had left him in good shape, for it was expressly stated that his prescription need not contain any musk, another useless physic reserved as a stimulant for the gravely ill, it being the custom for the respectable to die in an odour of musk as well as sanctity.

Pepys made a good recovery, being up after 2 weeks in bed, downstairs on the third week and walking nearly 2 miles by the end of the fourth week. He rode on horseback and was completely healed by the end of the sixth week from the day of the operation; but full control of the bladder returned very slowly.

Although Hollyer, perhaps unwisely, told Pepys he would not be troubled with stones again, he did, in fact, have further pains very suggestive of left renal colic. Hollyer told him it was "nothing but cold in my legs breeding wind", which consoled him for a year until he passed 2 small stones without pain and, hopefully for Hollyer's reputation, some wind. That was the end of Pepys's bladder troubles.

The 2 troublesome complications of cutting for stone were incontinence and fistula. Pepys was more fortunate than most and had neither, although 40 years after the operation and 3 years before his death, his wound reopened briefly.

Pepys was eternally grateful for his recovery and he celebrated it every year on 26 March, usually with a dinner followed by a musical afternoon, until his death at the age of 71 years. His stone he had mounted in a box specially made at a cost of 24 shillings and he displayed it at every opportunity.

One of the unfortunate consequences of this style of operation was damage to the vasa, with consequent sterility. In this respect Pepys suffered, the damage done no doubt compounded by the size of the stone that had to be dragged out. Though rendered sterile, he was far from impotent. Pepys loved the ladies—by his own free admission he could not resist a pretty face. His sexual appetites were strong.

His wife wrote "apart from heavy monthlies, we sleep together practically every night of our marriage, even during the alarms and excursions of the plague years and the Fire of London" (Delaforce, 1986).

Sir D'Arcy Power, the surgeon and biographer, suggested that the persistent irritation from scarring and infection of the perineal wound were responsible—a little fanciful perhaps (Power, 1933).

What did his wife think about things?

His wife was Elizabeth St Michael (Fig. 3), the pretty 15-year-old daughter of a refugee Huguenot, whom Pepys married when he was 22 years old.

During her courtship she noted his roving eye and, given half a chance, a roving hand as well. She wrote "I often wonder to myself as he is kissing me at midnight in our matrimonial bed, who else he has been kissing during the day". Although she accepted his almost daily peccadilloes, she drew the line at his seducing her friends and, even more vehemently, his own household staff, especially after she found him "*in flagrante*" with young Deb Willett, her companion.

So far as we know, he never attempted an affair with anyone of his own social standing, let alone with those above him. Prostitutes, bar-maids, shop girls and servants were his choice.

Over the years they employed a number of young maids, along with 4 companions for Elizabeth. He kissed, fondled, touched and pricked them all. He claimed his love of beauty drove him on. She said that to have the maid combing his hair and helping him to dress and undress was quite unnecessary. And yet he was insanely jealous of the amorous attentions paid to Elizabeth by the Duke of York (later James the Second) and his mentor, Lord Sandwich, by Elizabeth's dashing dancing master, John Pemberton, and even Pepys's servant and life-long friend, Will Hewer, who never put a foot wrong. Their relationship was tempestuous. He often called her a lazy beggar; she retaliated by calling him the worst words she could think of—a prick louse; he then blackened her eye and she responded by attacking him in bed with red hot fire tongs. Although tempestuous, it was a strong and wonderful marriage of 14 years' duration which she summed up as one of anger and grief, love and kindness. She died a few days after they returned from a trip to the Continent in 1669 of a fever, presumably typhoid. Pepys's last entry in his diary was "I shall miss her mightily in the long days to come".

Fig. 3 Elizabeth Pepys by John Hayls.

His greatest fame was yet to come. His diary, which he had started at the age of 27, he abandoned at the age of 36 for fear of losing his eyesight. It was, in fact, due to hypermetropia and slight astigmatism, a condition not correctable until the development of the cylindrical lens in 1820.

The diary was written in shorthand with sexual activities recorded—also in shorthand—in a polyglot of English, Spanish and French diluted with Latin (Fig. 4). It contained some of the hottest and

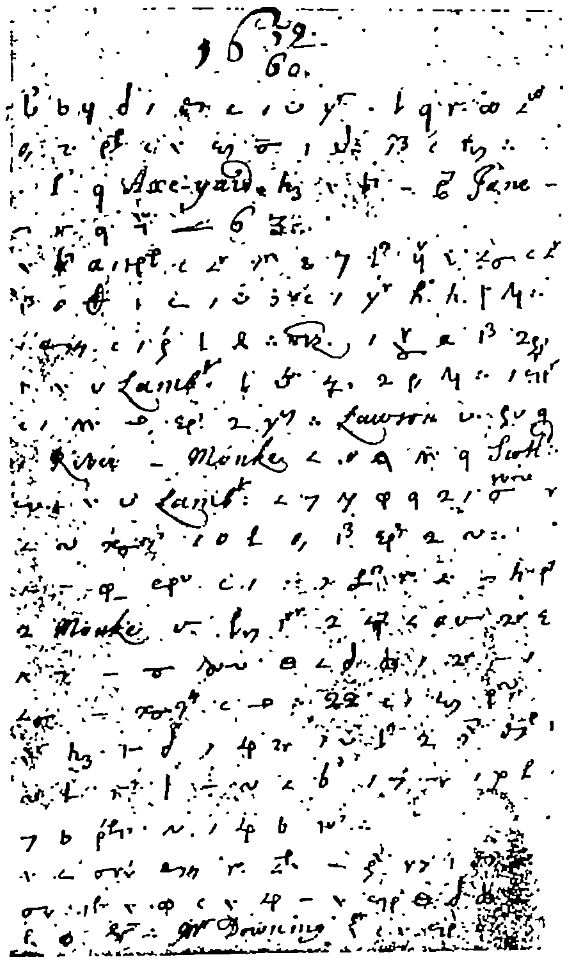

Fig. 4 The opening page of the Diary.

spiciest revelations ever to be published. Whether he meant it to be read after his death is not clear, but certainly 2 clues to the script were left with the diaries.

He bequeathed the diaries to his old college, Magdalene, Cambridge, where they languished untouched and unknown for 125 years. In 1825 the code was solved, they were translated and published to become a classic, one of the best known and best loved books in the language.

In the 34 years that he lived after Elizabeth's death he achieved many great distinctions—Master of a city company, Master of Trinity, President of the Royal Society, Member of Parliament—but his post of greatest renown was Secretary to the Navy, which earned him the affectionate title of "Father of the British Navy". He had a house full of fine things and a bank balance which ran into thousands.

So, after three score years and eleven, loaded with honours, he died. His literary collection was laid, complete with his diary, in his old college, where his youth might flower again. His body was laid beside that of his wife, Elizabeth, who had been buried in St Olaf's Church and had waited 34 years before being joined by him.

Perhaps it was right that he would never know that at autopsy his left kidney was seen to be disorganised and contained a nest of 7 stones, weighing four and a half ounces. His bladder was intact and stone-free.

His gratitude for a successful operation may be gauged from what he wrote: "I have cause to be joyful this day, it being my usual feast day for my being cut for the stone this day nine years and through God's blessing and at this day and have long been in as good condition of health as ever I was in my life or any man in England is, God make me thankful for it.

And so to bed".

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Rome Pouch: Pre-peritoneal Continent Ileal Reservoir with Hydraulic Valve

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Summary—We present our experience with a modified technique for constructing a continent ileal reservoir, using the terminal ileum in a pre-peritoneal position. The ureters were implanted using the Le Duc-Camey technique; the Benchekroun valve was used as a continence mechanism. This technique was used in 18 patients and its advantages and complications are discussed.

The continent enterocystoplasty, which uses an ileal reservoir anastomosed to the urethra (Camey, 1985; Goldwasser and Webster, 1985, 1986; Thuroff *et al*., 1986; Rowland *et al*., 1987; Benchekroun, 1977, 1987) as a substitute for the bladder, is of increasing interest to urological surgeons. This type of operation, however, has its limitations because of nocturnal incontinence in 30 to 40% of patients. In addition, it cannot be performed either in women or in patients with a neuropathic bladder when sphincteric malfunction is present. In such cases it is possible to use a continent urinary diversion (Kock *et al*., 1978; Kock, 1985; Lobel and Soret, 1987; Benchekroun *et al*., 1988). Unfortunately, these techniques have limitations in that protection of the upper urinary tract from reflux is not always satisfactory and the quality of the continence mechanism is not guaranteed; 20 to 30% of patients need further surgery. The first problem has been resolved by using uretero-ileal reimplantation techniques (Leadbetter, 1951; Turner-Warwick, 1976; Le Duc *et al*., 1987) and using detubularised bowel to give a low pressure. The problem of secondary incontinence, however, has not been completely solved and seems to be due to the efferent loop disinvagination which results from progressive enlargement of the reservoir (Fig. 1).

We have used a modification which prevents this progressive enlargement by placing the reservoir in a pre-peritoneal position, where adhesions develop and anchor it to the anterior abdominal wall. The Benchekroun valve, which we employ as a continence mechanism, is located at a distance from the reservoir by means of an antiperistaltic-ileal loop. This protects the valve from the effects of reservoir enlargement.

Patients and Methods

Eighteen patients have been treated: 13 (4 females and 9 males) for neuropathic bladder and 5 for bladder carcinoma.

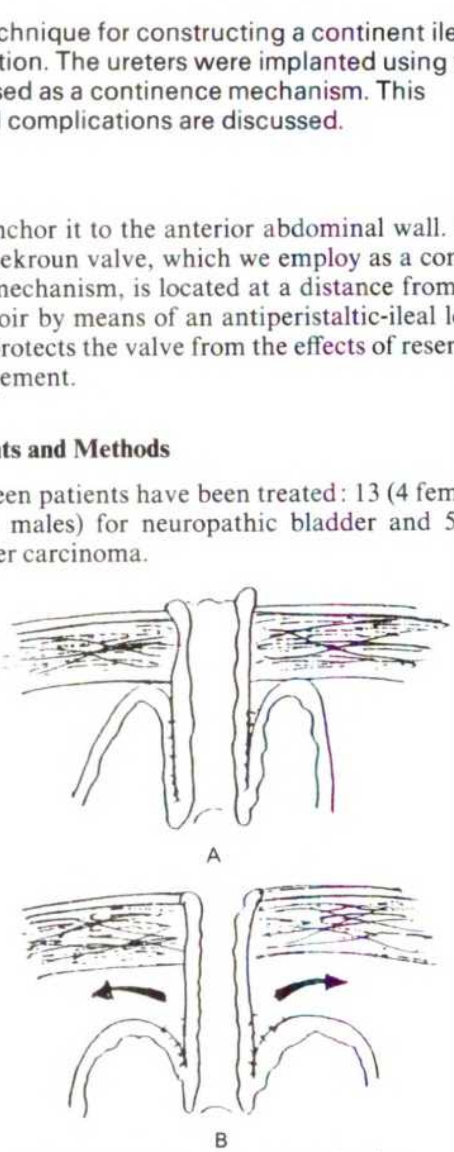

Fig. 1 Mechanism of efferent loop disinvagination.

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Of the patients with neuropathic bladder, 4 had myelomeningocele and 9 had traumatic lesions of the spinal cord. The indications for operation were complicated urinary fistulas (3 patients), urinary incontinence (3) and bilateral vesicoureteric reflux with hydroureteronephrosis (7). The mean age of the patients with neuropathic bladder was 27 years and 46 years for those with bladder carcinoma.

After performing cystectomy, a 70-cm ileal loop is isolated, 20 cm proximal to the ileocaecal valve. After re-establishing continuity of the bowel by end-to-end anastomosis, and performing appendicectomy, the ileal segment is positioned between the peritoneum and the abdominal wall. The peritoneum is closed behind the loop without traction on its mesentery (Fig. 2). The ileal reservoir is then prepared as follows: the right ureter is implanted into the first 10 cm (afferent loop), using the Le Duc-Camey technique (Fig. 3); the urinary reservoir is formed with the next 30 cm, which are detubularised along the antimesenteric border (Fig. 4); of the remaining 30 cm (efferent loop), 15 cm (the last 7 cm of which are freed from the mesentery) are intussuscepted using the Benchekroun procedure; the external stoma is then created and the Benchekroun valve is used to verify the most suitable position for the left ureteric implant. This is inserted into the remaining 15 cm of the efferent loop proximal to the reservoir. The Benchekroun valve is formed from the free end of the efferent loop sutured to the skin of the abdominal wall by interrupted Dexon 3/0 sutures. A 24 F catheter is inserted into the loop through the stoma.

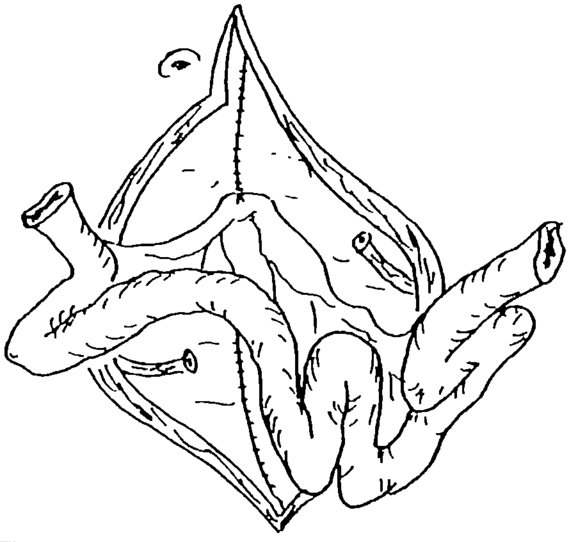

Fig. 2 Dislocation of ileal segment behind the peritoneum.

Two ureteric stents are then passed through the Benchekroun valve. Before closing the abdominal wall the urinary reservoir is sutured to the abdominal wall in the most suitable position for future catheterisation.

Three weeks later the drains are removed and self-catheterisation is started (6 to 7 times per day initially), reducing to 4 or 5 after 1 month (Fig. 5). Only absorbable sutures (Dexon) are used to make the urinary reservoir.

Results

Post-operative complications included necrosis of the Benchekroun valve in an obese patient, long-term stenosis of the uretero-ileal implantation and 1 disinvagination. The post-operative bladder capacity was 350 ± 60 ml, which increased to 600 ± 90 ml after 1 year. End pressure was 30 ± 10 cm H_2O. There was no ureteric reflux or fistula formation. During the first 15 days of self-catheterisation, 10 patients with pre-operative renal failure showed a transitory increase in blood urea nitrogen, but this was easily controlled by medical and dietetic treatment. The mean hospital stay was 28 days. Follow-up ranged from 12 months to 4 years. Continence of the valve remains excellent and there have been no complications with the stoma.

Discussion

The advantages of placing the reservoir in a pre-peritoneal position are as follows:

1. A low rate of disinvagination.
2. Secondary procedures on the uretero-ileal anastomosis or the valve are easier.
3. The development of adhesions around the reservoir and the ileal segment prevents dilatation of the reservoir and stabilises the length of the conduit, thus impeding disinvagination.
4. The distance of the valve from the reservoir and the antiperistaltic position of the efferent loop help to ensure continence.
5. The superficial position of the reservoir facilitates catheterisation.

This technique of continent diversion is particularly recommended for women and for patients with neuropathic bladders.

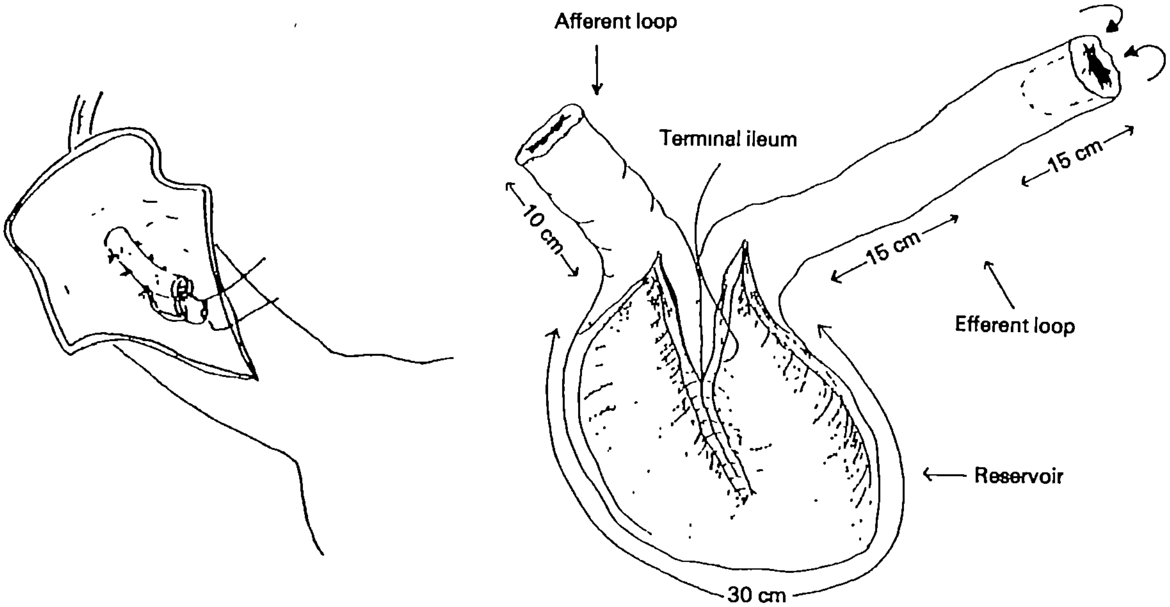

Fig. 3 Implantation of right ureter in the first 10 cm (afferent loop) using the Le Duc-Camey technique.

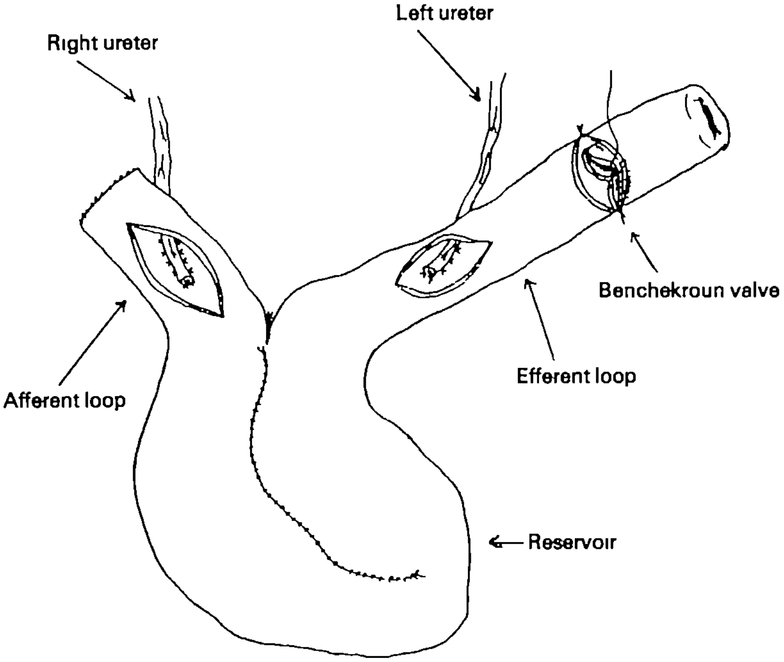

Fig. 4 The urinary reservoir is formed from the 45 cm of the detubularised ileum.

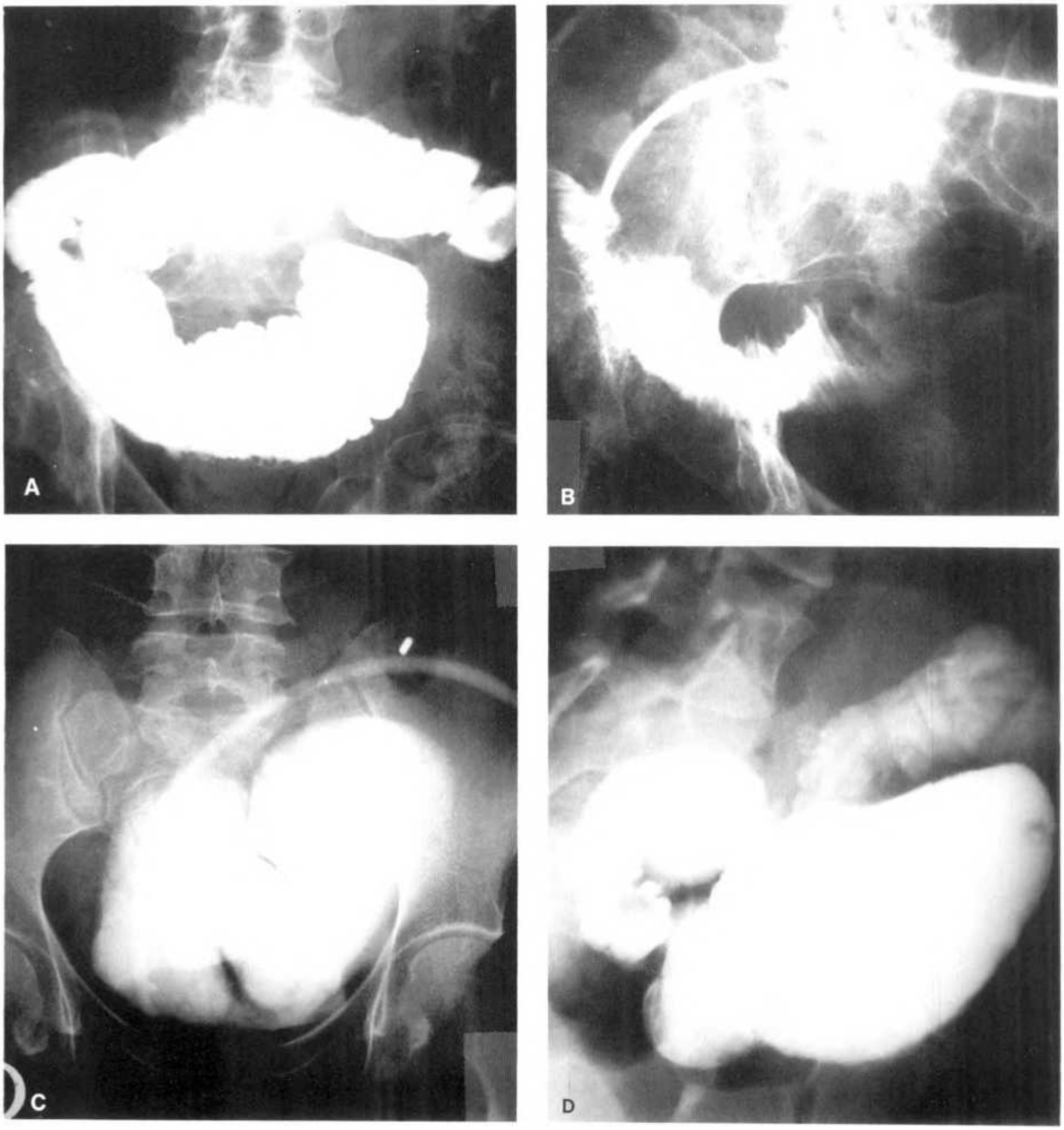

Fig. 5 Emptying of ileal reservoir under radiological control.

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HISTORICAL UROLOGY

Samuel Pepys and his Bladder Stone

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Summary—Samuel Pepys, as a young man, developed a bladder stone and, by the age of 25 years, realised that only surgery could deliver him from his agony. The chances of success in an age that was ignorant of sepsis were slender, but he opted for surgery. The operation, carried out through the perineum without anaesthetic by a master barber surgeon, was successful and Pepys survived. Although left sterile, he was far from impotent and he went on to achieve fame and fortune as Secretary to the Navy and President of the Royal Society. His greatest fame came after his death with the publication of his diary, which was to become one of the best known and best loved books in the language.

Most people have heard of Samuel Pepys, the celebrated diarist. Their knowledge of him may not be profound but they would know that he was an Englishman who had something to do with the Navy, who had a penchant for women and slavishly wrote down his everyday activities in a diary some 350 years ago.

He was born in London in 1633 of humble parents and, by sheer drive and hard work, eventually rose to become Secretary to the Navy and President of the Royal Society. Included among his friends and acquaintances were members of the royal family and the nobility.

His diary, which he kept as a young man for a period of 9 years, starting when he was 27, secretly and in shorthand, runs into 11 volumes. It is a record of his intimate thoughts and feelings.

Of all the incidents in his colourful life there was one which impressed him above all others. It was a surgical operation. Nothing cut deeper into his soul than did his few minutes in the hands of a surgeon. He rated the event above all other things in his life and observed each anniversary with solemn pomp until his death.

He had been plagued with excruciating pain from a bladder stone for a number of years and realised, by the age of 25, that he would have to do something about it. Surgery was the only option and he decided upon this. It was a courageous decision.

Pepys was a little man, squat, dark and decidedly ugly, unnecessarily busy, self-important and with the additional and slightly ludicrous dignity common in men of small stature. He was bright-eyed, sprucely dressed and he never entirely shook off his country speech (Fig. 1). Nevertheless, nearly all of those who knew him intimately liked and admired him. He was magnificent company and good humoured. He had astounding physical energy and industry and the hard struggle by which he won and retained his position left no trace of bitterness or disillusionment.

His day began at 4 a.m. He had one substantive meal a day—at noon—and was still working at midnight. He loved good food and wine and women—there was something pathological in his craving for the excitement of sex—yet he looked askance at dancing and disliked gaming, swearing and lack of observance on Sundays.

At the age of 20 and while still at Cambridge, he experienced violent renal colic and haematuria and lay for some days in agony. Enlightened lay opinion was that a stone had passed from his kidney into his bladder, where it lay forming a nucleus on

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Fig. 1 Samuel Pepys by John Hayls.

which there gradually formed a large calculus that 5 years later forced him to the surgeons.

Pepys came from East Anglia, where bladder stone was endemic. This was attributed to the cold north-east winds of East Anglia, the hard water and the high cereal diet (Riches, 1977). There was a strong familial history. His mother, brother and aunt all passed stones: "they make bloody water with great pain, it beginning just as mine." (Bryant, 1933).

Following the first attack he had a constant succession of fits of pain until the age of 25. "I remember not my life without the pain of stone in the kidneys, even the making of bloody water on extraordinary motion", he wrote (Shaw, 1970). The harsh winter of 1657 brought matters to a head. An operation could no longer be averted. Surgery was a dismal prospect—anaesthesia and asepsis unknown, death a possible outcome.

The technique for the removal of stone in Pepys's time evolved from the Marian operation, first described by Marianus Sanctus de Barletta in 1543 (Marianus, 1543). The approach was through the perineum into the bladder and a great number of instruments were used—hence its other title "The Greater Operation" or "Apparatus Major". The mortality rate was high, especially in adults. Ignorance of anatomy was the main cause of failure and frequently resulted in the incision entering the peritoneum or rectum, usually with a fatal outcome.

The early lithotomists were essentially commercial travellers, travelling from town to town looking for business. Diagnosis was uncertain and the more dishonest surgeons would keep a stone concealed in the palm of the hand to give to the patient should they not find one in the bladder. They were held responsible for their bad results and fined accordingly—in one case the fine was a sum sufficient to build a stone wall about the local churchyard—a Gilbertian touch (Riches, 1935).

Jacques de Beaulieu is one of the better known travelling lithotomists (Fig. 2). At one time he was a trooper in the French cavalry but he later adopted a semi-religious habit, took on the title of Frère Jacques and set out upon a life of cutting for stone throughout Europe. Following the removal of a stone, all spectators were asked to sign a certificate in his favour and with the incontestable remark "I have extracted the stone, I leave God to cure the patient", he withdrew and, like a true consultant, took no further part in the patient's post-operative management. When he had cut all that came his way in one place, he hastened to another (Riches, 1935).

After a career of fluctuating fortune he was presented by the magistrates of Amsterdam with a set of gold sounds. Although his personality and costume suggested something of a charlatan, his friends and enemies alike admitted his sincerity

Fig. 2 Jacques de Beaulieu, Frère Jacques (1651–1714).

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The Quality of Life after Radical Radiotherapy for Bladder Cancer

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Summary—The quality of life in 72 patients who had shown a complete response to radiotherapy, using a modified bladder symptom score and the Nottingham health profile, was compared with the quality of life in a similar control group matched for age and sex. There was no significant difference in either group.

The records of 69 patients who had undergone post-radiation salvage cystectomy were reviewed, looking specifically at surgical complications. There were 3 post-operative deaths (5%), 3 pulmonary emboli and 3 fistulae—with some overlap of complications. Five patients who underwent cystectomy for intractable symptoms in the apparent absence of recurrent tumour were found to have residual cancer in the excised specimens.

Previous studies have shown that approximately 50% of patients with muscle-invasive (T2/T3) transitional cell carcinoma (TCC) of the bladder have an initial response to radical radiotherapy, while the overall 5-year survival rate is 40% (Jenkins *et al.*, 1988; Wijkstrom *et al.*, 1992). In contrast, centres that rely on primary cystectomy have a 5-year survival rate of approximately 40% for pathologically staged T2/T3 bladder cancer (Montie *et al.*, 1984; Skinner and Lieskovsky, 1988; Stockle and Hohenfeller, 1991). Though there is little difference in these survival rates, it must be remembered that some patients treated by irradiation will invariably be understaged when compared with the pathologically staged cystectomy group.

Although radiation has the advantage that the patient retains his/her bladder, it is often criticised on the grounds that (a) post-radiation diarrhoea and cystitis so impair the quality of life that any improvement in survival is not worth the price, and (b) if the patient fails to respond or relapses later, the salvage cystectomy is a more difficult procedure and involves greater morbidity. We have assessed the quality of life in patients who showed a complete response to radiotherapy and have also reviewed the outcome of those who underwent salvage cystectomy to see if these criticisms are justified.

Patients and Methods

Seventy-two patients (mean age 70.7 years, range 40–90) who showed an initial complete response to radical radiotherapy for muscle-invasive bladder cancer were assessed. All received their radiotherapy between 1979 and 1990, representing 39% of the total number of patients who received radiotherapy for T2/T3 carcinoma of the bladder in this period. There were 57 males and 15 females; 34 patients had T2 and 38 had T3 TCC. The criteria for response were based on clinical, radiological and histological findings in the follow-up period. There was a mean follow-up of 5.2 years (range 16–160 months).

Fifty-five patients (mean age 69.9 years, range 37–83) were used as a control group. There were 42 males and 13 females. They were all in-patients in other surgical departments at the Royal London Hospital and had no prior history or urinary or bowel disease.

A modified bladder symptom score (Madsen and Iversen, 1983) was used to provide a quantified

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assessment of bladder symptoms (Fig.). This was completed by 2 of the authors (W.J.L. and B.J.J.) whilst directly questioning the patient.

The Nottingham health profile was completed by the patient alone. It is a well established evaluation of general quality of life (Hunt *et al.*, 1986).

The records of 69 patients who had undergone post-radiation salvage cystectomy were also reviewed, looking specifically at surgical complications. The group included 58 males and 11 females with a mean age of 62.5 years (range 34–80). There were 45 T2/T3 and 24 T4 tumours.

Haematuria:	0:	Never
	1:	Occasionally passes blood
	2:	Clots in urine
	3:	Clot retention
Frequency:	0:	>3 h
	1:	2–3 h
	2:	1–2 h
	3:	<1 h
Nocturia:	0:	0–1 x
	1:	2 x
	2:	3–4 x
	3:	>4 x
Urgency:	0:	None
	1:	Mild
	2:	Moderate (cannot stay in traffic jam)
	3:	Severe (can barely make it across room)
Dysuria	0:	No
	1:	Occasional burning
	2:	Burning >50% of the time
	3:	Frequent and painful burning
Incontinence:	0:	No
	1:	Yes
Rectal symptoms:	0:	None
	1:	Mucus
	2:	Occasional diarrhoea
	3:	Frequent diarrhoea
	4:	Incontinence

Fig. Modified bladder symptom score.

Results

The mean total symptom score for the radiotherapy group was 2.49 ± 0.404 compared with a mean of 2.073 ± 0.291 in the control group. Statistical analysis was performed using Student's *t* test. There was no significant difference between the 2 groups ($P = 0.422$).

Table 1 Individual Symptom Scores. Statistical Analysis Using Student's *t* Test

	Mean Scores		
Symptom	*Radiotherapy*	*Control*	*P*
Haematuria	0.286	0.049	0.042
Frequency	0.735	0.690	0.816
Nocturia	0.939	0.714	0.279
Urgency	0.204	0.357	0.301
Dysuria	0.163	0.143	0.819
Incontinence	0.041	0.095	0.302
Rectal symptoms	0.122	0.024	0.209

Individual symptom scores are listed in Table 1. There was no significant difference in any individual score. Table 2 shows the number of patients in both groups who complained of symptoms which could be classified as being more than mild; this usually corresponded to a symptom score >1 for that particular symptom. It can be seen that each group contained a similar number of patients with annoying symptoms.

Table 2 Patients with more than Mild Symptoms as Assessed by the Modified Scoring System (*i.e.* >1)

	No. of patients	
Symptoms	*Radiotherapy*	*Control*
Haematuria	2	0
Frequency	9	7
Nocturia	12	8
Urgency	2	1
Dysuria	1	1
Incontinence	0	0
Rectal symptoms	0	0

It was surprising to find that 3 patients in the control group admitted to haematuria when questioned: they were investigated for haematuria, including intravenous urography, urine cytology and cystoscopy and were found to be tumour-free.

Nottingham health profile assessments were identical in both groups.

Sixty-nine patients underwent salvage cystectomy following radiotherapy between 1970 and 1980. There were 3 post-operative deaths (5%). Major complications included: pulmonary embolus (3) (1 of whom died); loop necrosis (1); DVT (1); fistulae (3) (1 patient died and 1 had a late vaginal fistula which closed spontaneously with conservative management); prolonged ileus (2).

Five patients in this group had been thought to be free of tumour and underwent cystectomy for the control of intractable symptoms. When the bladder was subsequently examined histologically, all 5 had active cancer that had not been detected on previous biopsies.

Discussion

This study has revealed no difference in bladder symptoms between post-radiotherapy patients and a similar control group. Moreover, there was no difference in the Nottingham health profile. Patients who show a complete response to radiotherapy in the treatment of bladder cancer can reasonably expect little change in the quality of their life.

Salvage cystectomy has an acceptable morbidity. It is important to note that 2 of the 3 post-operative deaths occurred in patients who underwent cystectomy as a desperate attempt to control local symptoms in rapidly progressing disease. One of these patients eventually died of a pulmonary embolus and another had an internal enteric fistula, thus contributing to the post-operative complications. One of the remaining 2 fistulae occurred 10 months after cystectomy and closed spontaneously.

Another important and unexpected finding was that all 5 patients who had a salvage cystectomy for intractable symptoms had active cancer. Those who have severe post-radiation symptoms are likely to have residual tumour and should be offered salvage cystectomy sooner rather than later.

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Urologists' Attitudes to the Management of Bladder Cancer

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Summary—All consultant urologists in Great Britain and Ireland were sent 2 questionnaires relating to their management policies in bladder cancer; 82% and 78% respectively of questionnaires were completed and returned. The answers demonstrated a wide variation among urologists about the management of common clinical problems.

There is much controversy regarding the optimal management of patients with genitourinary malignancies (Moore *et al.*, 1990). Various options are available in the management of each stage of bladder cancer and in most cases the superiority of one mode of treatment over the other has not been clearly demonstrated in randomised clinical trials. The choice of management depends both on the personal preference of the surgeon and the patient and also on local treatment facilities. Moore *et al.* (1988) showed that British urologists had a more conservative approach to urological malignancies than their North American colleagues. This questionnaire study was carried out especially so that trainees would know what is practised throughout the country and also to help plan a clinical trial. Two questionnaires were sent to consultant urologists in which common clinical situations and a choice of treatment options were outlined.

Materials and Methods

The names of all consultant urologists in Great Britain and Ireland were obtained from the directory of the British Association of Urological Surgeons (BAUS). This list was amended to include recent appointments and 2 questionnaires were mailed separately to each urologist.

The questionnaires were sent with a covering letter asking the respondents to declare their actual and not preferred management. This letter indicated that questionnaire 1 was being circulated by trainees in urology in order to establish the current practice and questionnaire 2 was to help in the planning of a clinical trial. The questions gave different clinical scenarios with various management options (Tables 1–5). Enquiries were also made as to the availability of facilities such as flexible cystoscopy and urine cytopathology.

Results

A total of 278 urologists were contacted and after 2 months a reminder was mailed to those from whom no reply had been received; 229 replies were received to questionnaire 1 (82% response rate) and 217 to questionnaire 2 (78% response rate). All but 2 of the questionnaires had been completed as requested by consultants. Replies to the questions are shown in Tables 1 to 5.

Discussion

The good response to the questionnaires is gratifying and demonstrates the interest urologists have in this topic. We feel it is a valid method of assessing preferred treatment options and, since both teaching and district general hospitals in Great Britain and Ireland were included, the responses should be representative of current practice.

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Table 1 Questionnaire 1, Question 1

- For routine long term follow-up of bladder tumours, do you have access to a flexible cystoscope?

  Yes 179 (79%)
  No 48 (21%)

Which do you use most often if you have access to a flexible cystoscope?

	In males (%)	*In females* (%)
1 Rigid cystoscope + general anaesthetic	81 (46)	66 (38)
2 Rigid cystoscope + local anaesthetic	2 (1)	15 (9)
3 Flexible cystoscope + general anaesthetic	0 (0)	0 (0)
4 Flexible cystoscope + local anaesthetic	72 (41)	74 (42)
5 Combination of Rigid + GA & Flexi + LA	22 (12)	20 (11)

- For routine long term follow-up of bladder tumours, do you have access to a cytopathology service for urine examination?

  Yes 216 (94%)
  No 13 (6%)

If Yes do you use urine cytology in routine follow up of bladder tumours?

	(%)
Always	23 (11)
Sometimes	160 (74)
Never	33 (15)

Table 2 Questionnaire 1, Question 2

- A fit otherwise healthy 65-year-old male patient has a 3 × 3 cm bladder tumour which you completely resect. An EUA after resection reveals no residual mass Histology is reported as a moderately differentiated bladder tumour invading muscle (G2T2). Investigations, including CT scan, suggest no extravesical spread of the tumour

Which first line treatment would you recommend to the patient?

- If this had been a T3 tumour rather than a T2, would you select a different treatment option and which would it be?

	T2 (%)	*T3* (%)
(a) Radical TUR	71 (31)	2 (1)
(b) Primary cystectomy	13 (6)	18 (8)
(c) Radiotherapy then cystectomy	5 (2)	15 (7)
(d) Radiotherapy + salvage cystectomy (if evidence of residual tumour)	117 (51)	150 (66)
(e) Chemotherapy + b) or c) or d)	5 (2)	6 (3)
(f) Other	17 (7)	25 (11)

It is apparent that variation exists among urologists about the management of common clinical problems. This may be due to the availability of local facilities such as radiotherapy or may depend on the work load and referral practices in a particular area. It may also be due to differing interpretations of published results or may vary according to the audit of local results.

When planning clinical trials it is important to know what the standard treatment is before comparing this with a new treatment option. The results of this study have been considered by the Medical Research Council superficial bladder cancer subgroup in preparing a protocol for a trial that has recently been launched.

Although 79% of urologists have access to a

Table 3 Questionnaire 1, Question 3

- A 65-year-old otherwise healthy man complains of severe frequency, nocturia and occasional haematuria. His IVU is normal. Cytology is positive for malignant cells. Cystoscopy under GA reveals that 3/4 of the bladder is inflamed and the appearances are highly suggestive of carcinoma in situ (Tis)
  How many bladder biopsies would you take?

Biopsies	*No*	*%*
3	22	10
4	145	64
6	28	12

Would you biopsy the prostatic urethra?
Yes 86 (38%)
No 143 (62%)

- Biopsies are reported as showing multifocal Tis of the bladder only.
  Would you.

Use radiotherapy	10 (4%)
Perform cystectomy	52 (23%)
Use intravesical chemotherapy	169 (73%)

- If the prostatic biopsies had shown in situ carcinoma, which of options above would you perform?

Use radiotherapy	16 (11%)
Perform cystectomy	104 (70%)
Use intravesical chemotherapy	29 (19%)

Table 4 Questionnaire 2, Question 1

- In a fit patient with a pT1G3 tumour of the bladder which is single (or single with satellites) at first presentation or recurrence, without widespread carcinoma in situ, would your standard treatment be

1 TUR alone + follow up	186 (86%)
2 Intravesical chemotherapy (IVC)	4
3 Intravesical BCG	2
4 Radiotherapy	23 (8%)
5 Cystectomy	2
6 Other	0

Would your treatment differ if there were multiple tumours?
Yes 105/186 (56%)

- *Would your choice of treatment be influenced by finding concomitant, asymptomatic carcinoma in situ in mucosal biopsies?*
  These answers are for those selecting TUR alone (n = 186)
  Yes 149/186 (80%)

Changed treatment choices	*Multiple*	*Cis*
Intravesical chemotherapy	56	60
Intravesical BCG	23	56
Radiotherapy	23	9
Cystectomy	9	30
Other	3	1

Table 5 Questionnaire 2, Question 2

- Would you be interested in entering patients into an MRC study of radiotherapy versus standard therapy for pT1G3 tumours?
  Yes 150 (69%)
  No 67 (31%)
- What would you be prepared to adopt as standard treatment for the non-radiotherapy arm?

Standard treatment options chosen by the 150 interested in entering patients

TUR alone	118
IVC	72
BCG	50
Cystectomy	16
Chemotherapy	1

flexible cystoscope, 46% of these use rigid cystoscopy under general anaesthesia in the follow-up of patients with bladder cancer.

The management of invasive bladder cancer in the United Kingdom has been influenced by the results of a prospective controlled trial conducted by the Institute of Urology (Wallace and Bloom, 1976; Bloom *et al.*, 1982). This trial compared the outcome of patients treated by pre-operative radiotherapy combined with radical cystectomy against radical cystectomy alone. The reported 3-year survival figures showed an advantage for the former group (45 versus 33%), while the 5-year survival figures fell to 38 and 29% respectively.

The present study has shown a marked difference between the treatment of T2 and T3 tumours, with radiotherapy being the commonest treatment option for both; 52% of patients with T2 disease and 73% with T3 disease are treated with radiotherapy.

It was found that 31% of urologists treated T2 disease by radical transurethral resection and 93% of this group would change their treatment if the tumour was T3. One must bear in mind, however, that errors may be made in the classification of bladder tumours. T2 and T3 tumours cannot be differentiated on histological criteria alone because transurethral specimens do not always provide full thickness of bladder muscle and cannot be orientated. Magri (1962) suggested that T2/T3 tumours were more often understaged (27%) than overstaged (12%). Furthermore, Chisholm *et al.* (1980) argued that it was difficult to distinguish between T2 and T3 tumours and they grouped them into a single category.

Intravesical chemotherapy is the commonest treatment for patients with carcinoma *in situ* and

BCG is the agent most widely used; 23% of patients are offered cystectomy and 4% are treated with radiotherapy. The experience of Riddle *et al.* (1976) with only 11 patients suggests that radiotherapy has little to offer patients with symptomatic carcinoma *in situ*. The presence of carcinoma *in situ* in the prostatic urethra poses a difficult clinical problem, with cystoprostatectomy being one of the treatment options.

The review by Birch and Harland (1989) appears to have had little influence on the management of the pT1 G3 tumour, as transurethral resection alone is the most commonly practised management policy. There is considerable diversity if the tumour is multifocal or if there are areas of carcinoma *in situ*.

In this study we have not attempted to imply that one form of treatment is superior to another, but have simply presented the preferences expressed by urologists. It is clear that management decisions are influenced by local treatment facilities and are tailored to suit each clinical situation. A survey of this nature must therefore be limited in its accuracy, since factors other than those presented here may influence patient management. We feel, however, that these results provide an interesting indication of the preferred management of common urological dilemmas.

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Irrigation or No Irrigation after Transurethral Prostatectomy?

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Summary—Urologists remain divided as to the need for routine irrigation following transurethral prostatectomy (TURP). This randomised prospective study compared a policy of irrigation with that of no irrigation in a consecutive group of 200 patients undergoing TURP. In the irrigation group, a mean of 15 litres of irrigating fluid was used in each patient and one-third of patients required at least one bladder washout. In the no irrigation group, although two-thirds of the patients required at least one bladder washout, only one-third required more than one washout. No significant difference in blood loss, electrolyte balance, infection rate or recovery was seen in the 2 groups. This study led to a local change in practice, converting from a policy of routine irrigation to one of no irrigation.

Irrigation after transurethral prostatectomy (TURP) is a well established and widely used technique designed to reduce post-operative clot retention. However, urologists remain divided as to the need for post-operative irrigation, some relying on simple urine flow, with or without a forced diuresis (Essenhigh and Eustace, 1969).

Although the use of irrigating fluid may reduce the incidence of clot retention, it is costly and restricts the patient's mobility; it has been suggested that it may delay haemostasis and increase the risk of the TUR syndrome, particularly if a blocked catheter is not recognised quickly.

Supporters of no irrigation argue that clot retention is uncommon and feel that normal urine flow is sufficient to avoid the formation of clots in the bladder. But an increased need for bladder washouts may increase the incidence of post-operative infection.

We report the results of a randomised prospective study to compare the use of irrigation with no irrigation in a consecutive group of patients undergoing TURP.

Patients and Methods

Between February and July 1991, 200 consecutive patients undergoing TURP were randomised to be managed by irrigation or no irrigation post-operatively.

At the end of the operation, once the surgeon had achieved satisfactory haemostasis, a 3-way 22F plastic Foley catheter was inserted and the patient randomised to irrigation or no irrigation. If no irrigation was drawn, the irrigating limb of the catheter was closed with a spigot and the patient given a single dose of 20 mg frusemide intravenously. In the other patients, irrigation was with normal saline.

All patients were given one dose of intravenous gentamicin at the time of induction of anaesthesia. The surgeon was given the option to withdraw a patient from the study at any time.

The results were analysed by the Mann-Whitney U test.

Results

In all, 100 patients were managed by no irrigation and 99 by irrigation (1 patient was withdrawn because he required a laparotomy for bladder

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Read at the 48th Annual Meeting of the British Association of Urological Surgeons in Bournemouth, June 1992

perforation). No other patients were withdrawn from the study or deviated from the study protocol.

The 2 groups were comparable in terms of the indications for surgey, the type of anaesthesia and the weight of prostatic tissue resected (Table 1); 35 patients (17%) had infected urine pre-operatively.

Table 1 Details of Patients

	Irrigation	*No irrigation*
No. of patients	99	100
Benign/malignant	68/31	73/27
Elective/retention	55/44	56/44
Anaesthetic: spinal/general	49/50	40/60
Mean weight of resected prostate (g)	31	31
Pre-operative infection	16	19
Mean pre-operative haemoglobin (g/dl)	13.4	13.3

Sixty units of blood were given to 23 patients in the irrigation group and 52 units to 19 patients in the no irrigation group (Table 2). There was no statistically significant difference in the mean fall in haemoglobin, haematocrit or serum sodium as measured pre-operatively and on days 1 and 3 post-operatively. Over 90% of all patients showed a fall in serum sodium post-operatively.

A total of 1436 litres of normal saline was used for irrigation in 99 patients, delivered from 2-litre bottles or 3-litre bags (Table 3). The irrigant was used mostly in the recovery room or in the immediate post-operative period (day 0). The mean volume of irrigant per patient was 15 litres.

More washouts were required in the no irrigation group (Table 4) and 36 of the 100 patients needed more than one bladder washout. However, despite the use of irrigant, 33 patients in the irrigation group still required at least one bladder washout.

Table 2 Blood Measurements Pre-operatively and on Days 1 and 3 Post-operatively

	Irrigation	*No irrigation*
Mean haemoglobin (g/dl)		
Pre-operative	13.4	13 3
Day 1	11.7	11.9
Day 3	11 5	11.7
Mean haematocrit		
Pre-operative	0 39	0 40
Day 1	0 34	0.36
Day 3	0 34	0.35
Mean serum sodium (mmol/l)		
Pre-operative	140	138
Day 1	136	135
Day 3	136	136

Table 3 Amount of Irrigation Fluid Used in 99 Patients

	Irrigation fluid (litres)	
	Total	*Mean volume/patient/day*
Recovery	783	8
Day 0	438	6
Day 1	137	3
Day 2	37	4
>Day 2	41	8

Table 4 Number of Bladder Washouts

	Irrigation		*No irrigation*	
	No. of washouts	*No. of patients*	*No. of washouts*	*No of patients*
Recovery	8	8	55	28
Day 0	30	17	74	34
Day 1	17	10	26	23
Day 2	11	7	3	3
>Day 2	13	7	10	2

One patient in each group had to return to theatre in the immediate post-operative period for continued bleeding and one patient in the irrigation group returned after 8 days because of persistent clots in the bladder.

No statistically significant difference in time of catheter removal or length of post-operative hospital stay was seen in the 2 groups (in 13 patients the post-operative stay was considered to be excessively long (due to an unrelated cause) and these patients were excluded from the analysis) (Table 5). Eight patients in the no irrigation group and 6 in the irrigation group had infected urine post-operatively when urine was cultured on days 1 and 3. Only one of these patients had been shown to have a pre-operative urine infection.

Discussion

A Regional Urology Audit Meeting is organised 3 times a year in the South East Thames Region and attended by representatives from each of 14 districts which have consultant urologists. A questionnaire was circulated to consultant urologists to consider their different practices across the region. This revealed that only 1 of 14 districts had a policy of not irrigating after TURP but this district reported no problems with adopting such a policy.

Adopting a policy of irrigation or no irrigation after TURP did not affect post-operative bleeding or recovery time. No significant difference in blood

Table 5 Post-operative Course

	Irrigation						*No irrigation*					
Median post-operative stay (days)				5					5			
Time of catheter removal	Day	1	2	3	4	>4	Day	1	2	3	4	>4
No. of patients		1	33	43	10	12		2	41	36	11	10
Post-operative infections				6					8			

loss was seen in the 2 groups and, overall, 42 patients (21%) required transfusion, in keeping with the results of other studies (Malone *et al.*, 1986). The catheter was removed when the urine was considered to be clearing and free of clots and no significant difference in the time of catheter removal was seen. The median post-operative stay in both groups was 5 days.

In the no irrigation group, two-thirds of patients required at least one bladder washout and one-third required more than one. This is a much higher figure than that reported in a previous series where only 15% required any bladder washout and only 2% had more than 2 washouts (Malone *et al.*, 1986). This may reflect our inexperience with the technique or may indicate that we were more liberal in our use of bladder washouts, not simply restricting their use to patients with clot retention. Using irrigation did not totally avoid the need for washouts. In the irrigation group, one-third of patients still required at least one bladder washout and 18% required more than one.

It has been suggested that the increased opening and flushing of the sterile closed-catheter system with bladder washouts results in increased contamination and infection. Despite the large number of bladder washouts, the infection rate in this series was low (7%) and lower than that reported by Malone *et al.* (1986), even though 44% of patients had an indwelling catheter pre-operatively and 18% had a pre-operative infection. The low post-operative infection rate probably reflects our use of prophylactic gentamicin peri-operatively. Comparing the 2 groups of patients, there was no correlation between infection and the number of bladder washouts.

The average amount of irrigant used post-operatively was 15 litres per patient, a figure similar to that used peri-operatively by Ghanem and Ward (1990). The use of irrigation incurred an extra cost of £13 per patient, taking into account the cost of the irrigant and also the cost of the extra bladder washouts needed in those without irrigation. In Brighton Health District a bladder washout is costed at £2.15 (based on a reusable bladder lavage pack £1.32, 1 litre of sterile water £0.64 and a pair of sterile gloves £0.19) and normal saline for irrigation costs £3.19 per 3-litre bag; £13 is a small proportion of the total cost of an in-patient prostatectomy, but nevertheless would represent an annual saving of £5000 to £6000 if Brighton adopted a no irrigation policy.

For many years we have used irrigation routinely following TURP. At the conclusion of this study our nursing and medical staff favoured converting to a policy of no irrigation and in most cases this is now our practice.

This study provides an example of a topic which has completed the audit cycle. The idea arose from a Regional Audit Meeting, was run as a prospective clinical trial within the region and has resulted in a change in patient management.

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Local Hyperthermia for Prostatic Disease: *in vitro* Studies on Human Prostatic Cancer Cell Lines

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Summary—Local hyperthermia for benign and malignant prostatic disease remains largely empirical. In an attempt to understand the biological action of hyperthermia, and its potentiation by antiandrogen seen in clinical practice, the interaction of the two has been studied in prostatic cancer cell lines.

Human prostatic cancer cell lines LNCaP and DU 145 were studied to examine the effects of heat shock treatment (HST), androgen (5α-dihydrotestosterone: 5αDHT) and antiandrogen (hydroxyflutamide: OH-Flut) on cell growth and survival. Response (measured as increased DNA content) to 5αDHT demonstrated that LNCaP was androgen sensitive, whereas DU 145 was androgen insensitive; OH-Flut stimulated LNCaP growth but had no effect on DU 145 growth. Thermotolerance was exhibited by DU 145 cells but not by LNCaP cells. The combination of HST followed by OH-Flut markedly reduced survival of LNCaP cells compared with HST alone. This effect was not observed in DU 145 cells. The enhanced cytotoxic effect of antiandrogen and hyperthermia could minimise the effect of thermotolerance in malignant cells surviving initial hyperthermia treatment and might suggest real clinical value for the combination or sequence.

Prostatic cancer is the second most common cause of death from malignant disease in men. Although it is usually the systemic disease that eventually results in the patient's death, locally advanced disease may be associated with severe morbidity. For these patients radical surgery is inappropriate. The therapeutic options currently available include hormonal manipulation, radiotherapy or transurethral resection. There is a need for new simple, safe and effective forms of treating local progression. Clinical studies have already demonstrated that local prostatic hyperthermia may have a dramatic effect on local and systemic malignant prostatic disease (Mendecki *et al.*, 1980).

Hyperthermia will result in cell death if high temperatures are used, but in clinical practice the temperature is limited by the risk of injury to adjacent normal tissues. Temperatures used (43–46°C) will not result in the death of all cells, and those that survive initial heat exposure will become resistant to subsequent heating due to the development of thermotolerance. This phenomenon is mediated through the production of a group of proteins known as heat shock proteins (hsp). Local prostatic hyperthermia for prostatic disease remains largely empirical. In an attempt to understand the biological action of hyperthermia, and its potentiation by antiandrogen reported in clinical practice in benign disease (Lindner *et al*, 1990), the effects of hyperthermia have been studied in the prostatic cancer cell lines LNCaP and DU 145.

Materials and Methods

Two human prostatic cancer cell lines (kindly supplied by Dr C. Eaton, Tenovus Institute for Cancer Research, Cardiff), LNCaP (Horoszewicz *et al.*, 1978) and DU 145 (Stone *et al.*, 1978), were studied to examine the effects of hyperthermia or heat shock treatment (HST), androgen (5α-dihydrotestosterone: 5αDHT) and antiandrogen (hydroxyflutamide: OH-Flut) on cell growth and survival.

Based on the Bard Lecture given by S. N. Lloyd at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

We have previously shown that total DNA content correlates with total cell number (Field, 1985) in experiments in which cells were plated down at about 20% confluence into multiwell plates and grown in 5% heat inactivated dextran coated charcoal for up to 96 h (Leake *et al.*, 1987). Cells were plated thus in 6-well plates and allowed to rest for 24 h before each experiment was started. Total DNA content was evaluated 24 h (Day 1) and 48 h (Day 2) following HST. DNA content was determined by the Hoescht method (Leake and Habib, 1987). Absence of cell growth over the first 24-h period following HST could equally reflect either cell damage or dormancy. However, reappearance of cell growth and DNA synthesis over the second 24-h period was taken as an indication of cell viability. Correspondingly, a reduction of DNA synthesis after heat exposure indicated either cell death or heat induced growth inhibition.

Effects of HST on cell survival

HST was delivered to cells in flasks in a thermostatically controlled water bath (Fig. 1). All cells were cultured for the same time interval but were exposed to different heat regimens, the cells being maintained at 37°C between exposures. Control cells were maintained at 37°C throughout. The 2 heat regimens chosen were (a) 2 hours' exposure to 42°C (HST 42) and (b) 39°C for 2 h followed by a 12-h recovery period followed by 2 hours' exposure to 42°C (HST 39+42).

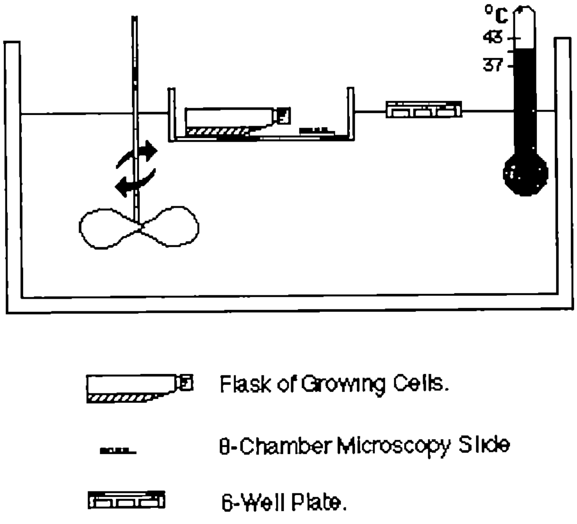

Fig. 1 Diagram of thermostatically controlled water bath for delivering HST.

Effects of 5αDHT and OH-Flut on cell growth

To establish the androgen and antiandrogen sensitivities of the 2 cell lines to exogenous ligands, cells were cultured for 48 h in the presence of increasing concentrations of 5αDHT or OH-Flut. The concentration range tested was between 10^{-14} and 10^{-6} M.

Effects of HST and OH-Flut in sequence on cell survival

Some cells were exposed to OH-Flut for 48 h, some to HST 39+42 alone and others to HST 39+42 followed by OH-Flut for 48 h. All cells remained in culture for the same period and were harvested concurrently.

Statistics

All graphs were plotted using the software Cricket Graph version 3.2. Statistical comparisons between the effects of HST on cell survival were made using the 2-sample Student's t test and the effects of HST and OH-Flut alone and in combination were made using the method of analysis of variance using Minitab software version 6 for Apple Macintosh. A P value of <0.05 was regarded as statistically significant.

Results

Effect of HST on cell survival

Each data column represents the mean value of duplicate experiments (+SD), each performed in triplicate. Exposure to 42°C for 2 h was cytotoxic to DU 145 cells as seen by the reduction in DNA content on Day 2 (Fig. 2) ($P<0.001$), but prior exposure to the lower temperature of 39°C enabled cells to survive and continue to grow after 2 h at 42°C, though total growth was slightly reduced compared with controls. LNCaP cells survived the higher temperature of 42°C but DNA content was markedly reduced. However, if exposure to 42°C was preceded by prior exposure to 39°C, the growth recovered almost to control levels (Fig. 3).

Effects of 5αDHT and OH-Flut on cell growth

Quadruplicate controls were used for each experiment and each data point represents the mean value of duplicate experiments, each performed in triplicate (±SD). Neither 5αDHT nor OH-Flut appeared to effect growth of DU 145 cells (Fig. 4), but LNCaP cells were stimulated to grow in the presence of both ligands over the ligand concentrations tested (Fig. 5).

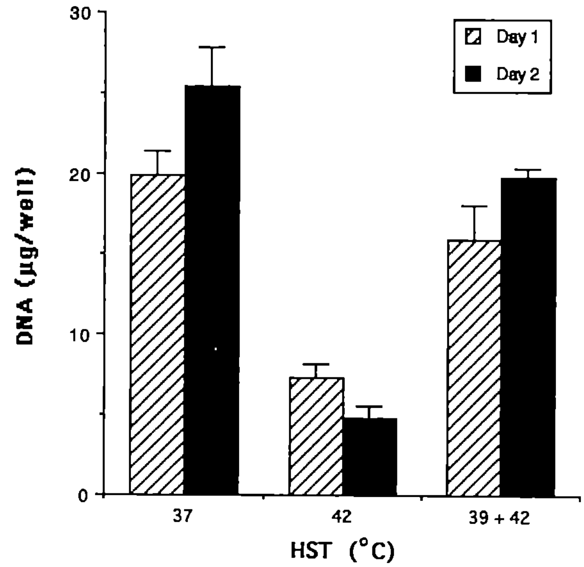

Fig. 2 Effects of heat shock treatment (HST) at 42°C alone and at 39°C+42°C, compared with 37°C controls on survival of DU 145 cells. Each data column represents the mean value of duplicate experiments (+SD), each performed in triplicate.

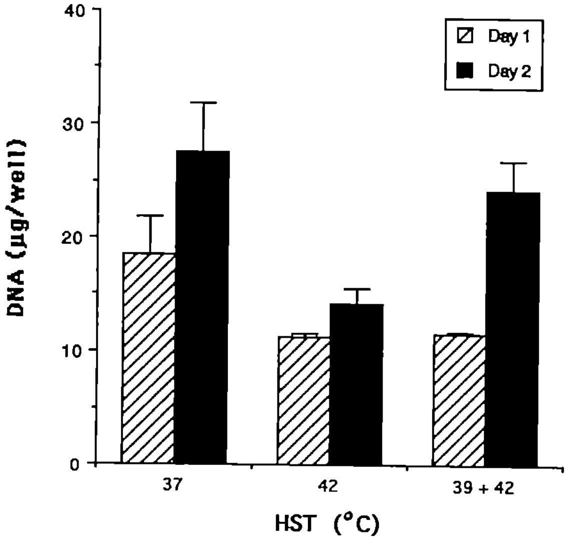

Fig. 3 Effects of heat shock treatment (HST) at 42°C alone and at 39°C+42°C, compared with 37°C controls on survival of LNCaP cells. Each data column represents the mean value of duplicate experiments (+SD), each performed in triplicate

Effects of HST and OH-Flut in sequence on cell survival

Each data column represents the mean value of duplicate experiments (+SD), each performed in triplicate. When cells were first exposed to the 39°C followed by the 42°C regimen (HST 39+42), then treated with OH-Flut (10^{-9} M) for 48 h, total DNA content was reduced by 23% in LNCaP cells compared with cells treated to (HST 39+42), then grown over the same time period in the absence of OH-Flut ($P<0.001$) (Fig. 6). It appeared that HST altered the response of the cells to OH-Flut, converting the latter's partial agonist effect into a synergistic antagonist one. These effects were not observed in the androgen insensitive cell line DU 145 (Fig. 7) ($P>0.05$).

Discussion

These experiments were designed as a model to investigate the effects of hyperthermia on the survival of prostatic cancer cells. It is apparent that different cell lines (and thus different tissues) have different thermal sensitivities. We have been able to demonstrate the development of thermotolerance as result of prior exposure of the cells to a non-lethal temperature. Thermotolerance is a short-lived phenomenon, lasting only 2 to 3 days (Nielsen and Overgaard, 1982). The effects of thermotolerance could be minimised by using the highest temperatures possible that avoid damage to adjacent normal tissues, and if fractionation is used, treatment intervals should be more than 3 days apart.

The partial agonist effects of OH-Flut *in vitro* have been reported previously (Wilding *et al.*, 1989). Interaction of androgens and antiandrogens at receptor level by direct competition may be an oversimplification. One hypothesis involves the overcoming of negative control pathways (Sonnenschein *et al.*, 1989) and another the modification by anti-steroid of steroid receptor/hsp 90 complex interactions (Baulieu, 1987). Under normal circumstances hsp 90 molecules are thought to bind to the DNA binding domains of steroid receptors and the receptor/hsp 90 complex is assumed to be the stable form of "empty" receptor in the soluble compartment of the nucleus (King, 1992). Dissociation of the hsp 90/receptor complexes occurs in the presence of androgen leaving the DNA binding domains vacant for DNA binding with modification of gene expression. We postulate that the sequence of antiandrogen and hyperthermia leads to reduced androgen receptor/DNA interaction. This combined therapeutic approach may reduce the clinical effects of thermotolerance in prostatic cancer cells by reducing the overall number of viable cells.

There may be a role for local prostatic hyperthermia in the management of patients with locally

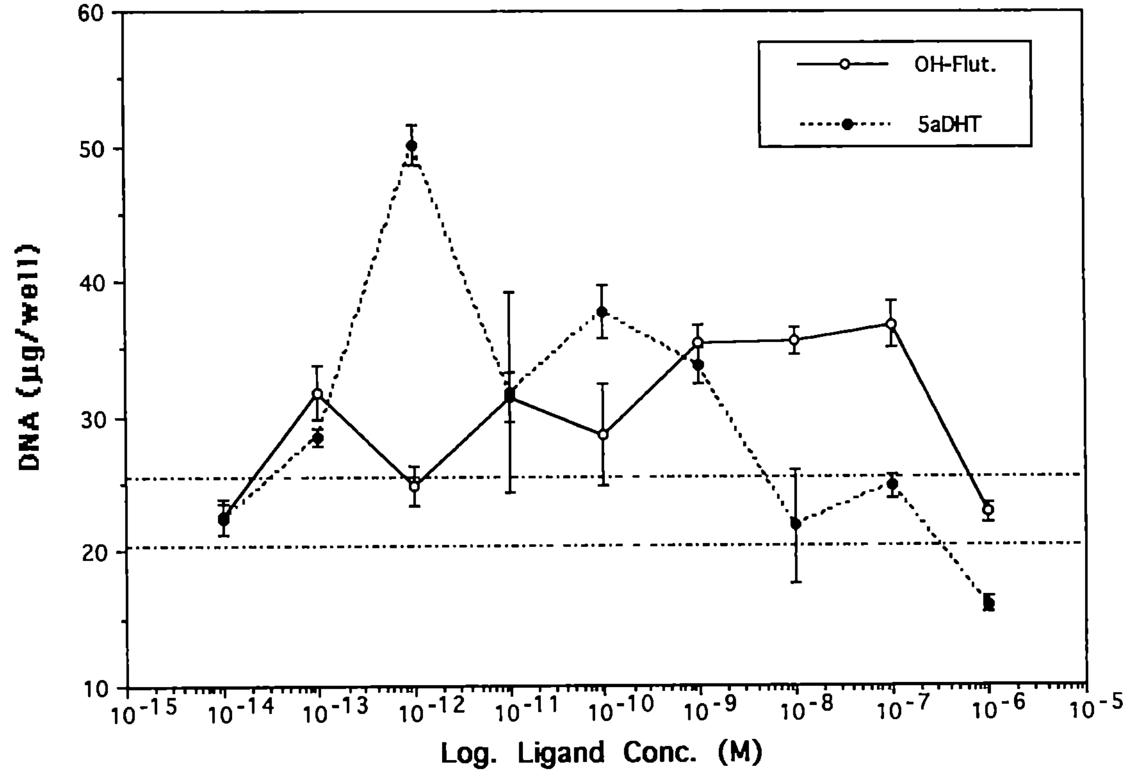

Fig. 4 DU 145 dose-response curves to 5αDHT and OH-Flut Cells were plated down for 24 h, the hormone added and total DNA content determined after a further 48 h. The horizontal dashed lines represent the mean of quadruplicate controls ± SD, each data point represents the mean value of duplicate experiments, each performed in triplicate.

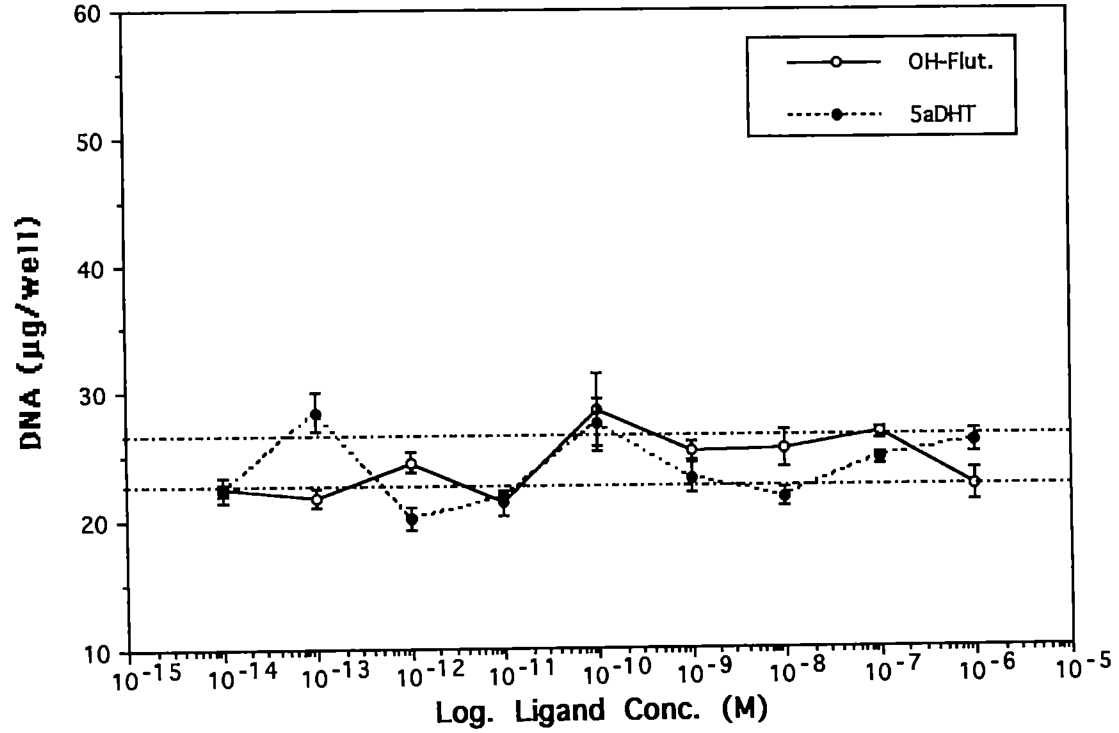

Fig. 5 LNCaP dose-response curves to 5αDHT and OH-Flut. Cells were plated down for 24 h, the hormone added and total DNA content determined after a further 48 h. The horizontal dashed lines represent the mean of quadruplicate controls ± SD; each data

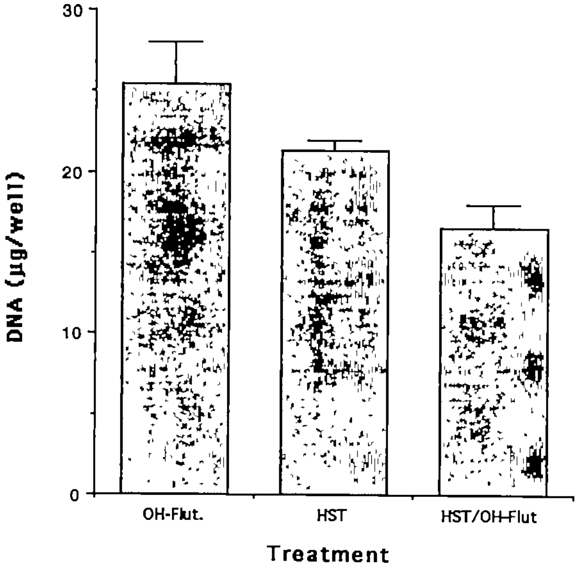

Fig. 6 LNCaP cells—comparison of the effects of OH-Flut (10^{-9} M), HST 39+42 and OH-Flut (10^{-9} M) followed by HST 39+42 on total DNA content. Corresponding wells were harvested 24 and 48 h after the end of treatment. Each data column represents the mean value of duplicate experiments (+SD), each performed in triplicate.

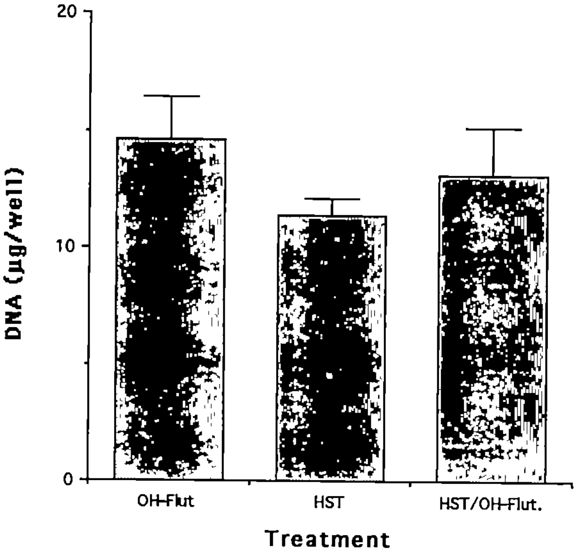

Fig. 7 DU 145 cells—comparison of the effects of OH-Flut (10^{-9} M), HST 39+42 and OH-Flut (10^{-9} M) followed by HST 39+42 on total DNA content. Corresponding wells were harvested 24 and 48 h after the end of treatment. Each data column represents the mean value of duplicate experiments (+SD), each performed in triplicate.

advanced prostatic disease. The effects of hyperthermia may be maximised by combining it with other established treatment modalities such as hormonal manipulation in patients with hormone sensitive tumours or with radiotherapy.

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Staging of Prostate Cancer. Accuracy of Transrectal Ultrasound Enhanced by Prostate-specific Antigen

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Summary—Transrectal ultrasound (TRUS) has shown some promise in the staging of prostate cancer, while prostate-specific antigen (PSA) alone is insufficient. By combining prospective TRUS evaluation with retrospective PSA analysis, we demonstrated an increased accuracy of this combined staging method over TRUS alone. In 48 men undergoing radical prostatectomy, TRUS was performed and PSA measured pre-operatively. On the basis of TRUS, tumours were classified as contained or uncontained. An "expected" PSA value was then calculated for each patient as follows:

$$K \times \text{volume of hypoechoic area} + 0.07 \times \text{prostate volume}$$

where $K = 2.1$ if the combined Gleason score of the initial biopsy was ≥ 7, or 4.2 if the score was ≤ 6.

If a patient's pre-operative PSA value was less than or equal to the expected PSA, his tumour was judged to be contained. Staging by both TRUS and PSA was combined, so that if the tumour was judged uncontained by either parameter, the combined prediction was uncontained. Results of the combined staging were: sensitivity 84%, specificity 82%, positive predictive value 94%, negative predictive value 60%, accuracy 83%. This PSA formula, which takes into account the size and grade of the lesion rather than an arbitrary cut-off value, enhances the local staging of prostate cancer by TRUS.

Accurate staging is crucial in evaluating treatment options and prognosis for the patient with prostate cancer. Clinical staging, however, is fraught with difficulties. The digital rectal examination frequently understages the tumour and computed tomography lacks sensitivity in defining local disease (Scardino *et al.*, 1989). Magnetic resonance imaging has recently been studied by a multi-centre group and demonstrated an overall 69% accuracy in staging local disease (Rifkin *et al.*, 1990). Transrectal ultrasound (TRUS), evaluated extensively for the staging of prostate cancer, has produced somewhat variable results (Table 1). Prostate-specific antigen (PSA) has also been examined for use in staging. Although several studies indicate a good correlation between PSA and tumour volume, the accuracy is not sufficient for its use as an independent predictor of stage (Table 2). Overall, a high degree of accuracy has not been achieved by any of the clinical staging modalities.

In the hope of developing a better method of local staging, we prospectively evaluated the combination of PSA and TRUS in patients undergoing radical prostatectomy. Using the combination of PSA and TRUS, we developed a formula to estimate whether an individual tumour was "contained" or "uncontained". This formula, which takes into account the volume of tumour as well as grade, appears to enhance staging accuracy.

Patients and Methods

The study group comprised 48 men: 43 patients from the San Francisco Veterans Administration

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Table 1 Studies Evaluating TRUS Staging Before Radical Prostatectomy

	Probe (MHz)	*No. of patients*	*Sensitivity (%)*	*Specificity (%)*	*PPV* (%)*	*NPV (%)*	*Accuracy (%)*
Extracapsular extension							
Pontes *et al.* (1985)	3.5	31	59	78	87	44	65
Salo *et al.* (1987)	5.0	31	86	94	92	89	90
Hardeman *et al.* (1989)	4.0	43	54	58	62	50	56
Andriole *et al* (1989)	7.0	64	50	90	55	89	83
Present study (1991)	7.5	48	51	92	94	41	63
Seminal vesicle involvement							
Pontes *et al* (1985)	3.5	27	33	100	100	84	85
Salo *et al.* (1987)	5.0	22	29	100	100	75	77
Hardeman *et al.* (1989)	4.0	38	60	89	67	86	82
Andriole *et al.* (1989)	7.0	64	20	100	100	94	94
Present study (1991)	7.5	48	57	100	100	85	88
All sites							
Perrapato *et al* (1989)	5.0–7.0	25	71	100	100	90	92
Andriole *et al.* (1989)	7.0	64	38	90	55	81	77
Rifkin *et al.* (1990)	5.0–7.5	219	66	46	63	49	58
Present study (1991)	7.5	48	54	100	100	39	65

*Definition of terms as in the text.

Medical Centre and 5 from the private practice of one of us (P.N.) at the University of California, San Francisco. Ages ranged from 59 to 75 years (mean 65). All patients underwent TRUS and PSA measurement as part of the pre-operative evaluation for radical prostatectomy. The study group was selected from 60 consecutive patients undergoing radical prostatectomy between February 1989 and October 1990. Twelve patients were not included because no hypoechoic lesion was seen on TRUS (3 patients), TRUS was incompletely performed (3) or TRUS was not performed (6). Five patients had stage A2 disease (2 with isoechoic lesions and therefore not included) and the rest had either stage B or C disease by digital rectal examination.

TRUS

In all but 2 cases, TRUS was performed by one of us (K.S.) with a 7.5 MHz biplanar (Teknar, Inc., St Louis, USA) or multiplanar probe (Diasonics, Inc., Milpitas, USA). Patients were examined in the left lateral decubitus position. The glands were routinely measured. Hypoechoic regions were considered suggestive of carcinoma and were also measured.

To estimate size, the longest diameter in each of 3 dimensions was marked on the scan and computed in centimetres. As TRUS underestimates the actual size of a focus of cancer by 0.4 cm (Shinohara *et al.*, 1989), this amount was added to each dimension of a hypoechoic lesion. Such a correction factor is not necessary for the calculation of whole prostate volume. The product of these 3 measurements was then multiplied by 0.52; this is the formula for the volume of an ellipsoid body. The result was expressed in ml:

Table 2 Studies Evaluating PSA Staging Before Radical Prostatectomy (> 10 ng/ml, uncontained. Tandem-R assay)

	No. of patients	*Sensitivity (%)*	*Specificity (%)*	*PPV* (%)*	*NPV (%)*	*Accuracy (%)*
Lange *et al.* (1989)	100	58	80	78	61	68
Brawer and Lange (1989)	60	52	77	68	62	65
Hudson *et al* (1989)	74	50	65	43	70	41
Partin *et al.* (1990)	350	41	89	76	63	67
Present study (1991)	48	46	91	94	33	56

*Definition of terms in text.

Table 3 PSA Values and Stage

Patient no.	*Actual PSA (ng/ml)*	*Biopsy grade*	*Nodule size (ml)*	*Prostate size (ml)*	*Predicted PSA (ng/ml)*	*PSA stage*
4	9.5	≤6	1.5	45	9.5	B
5	2.9	≤6	1.46	15	7.2	B
7	22.0	≥7	2.6	154	16	C
8	2.4	≤6	2.49	41	13	B
9	1.8	≥7	0.69	18	2.7	B
10	6.6	≥7	0.92	22	3.5	C
11	1.5	≥7	6.55	23	15	B
12	1.6	≤6	1.03	23	5.9	B
13	9.0	≥7	0.67	33	3.7	C
14	16.3	≤6	2.75	28	14	C
15	4.9	≤6	1.7	21	8.6	B
16	10.4	≤6	12.6	60	57	B
17	13.5	≤6	1.79	22	9.1	C
18	5.7	≥7	0.88	25	3.6	C
19	19.3	≥7	6.2	38	16	C
20	34.7	≥7	7.7	52	20	C
21	5.7	≥7	2.62	41	8.4	B
22	1.1	≤6	1.32	26	7.4	B
23	5.5	≤6	1.28	17	6.6	B
24	13.0	≥7	0.88	29	3.9	C
26	19.5	≤6	28.3	51	122	B
27	52.0	≤6	2.33	25	12	C
29	8.9	≥7	7.84	45	20	B
30	6.7	≤6	2.3	26	12	B
31	29.5	≤6	3.84	42	19	C
32	14.8	≤6	1.54	29	8.5	C
34	2.4	≥7	30.0	40	65	B
35	6.3	≥7	1.28	26	4.5	C
36	58.6	≥7	5.2	17	12	C
37	6.6	≤6	2.75	32	14	B
38	4.6	≥7	1.02	28	4.1	C
39	4.8	≥7	2.84	35	8.4	B
40	14.5	≥7	1.06	34	25	B
41	25.0	≥7	7.99	60	21	C
42	85.0	≥7	10.0	25	23	C
44	5.7	≤6	1.05	87	11	B
46	7.3	≥7	2.33	27	6.8	C
47	2.9	≤6	1.75	25	9.1	B
48	4.4	≤6	0.57	26	4.2	C
49	6.4	≥7	3.68	24	9.4	B
50	9.5	≤6	5.25	56	26	B
51	19.9	≤6	3.04	23	14	C
52	31.0	≤6	3.77	40	19	C
54	9.7	≤6	1.0	21	5.7	C
55	7.0	≤6	2.16	33	11	B
56	3.1	≤6	0.47	30	4.1	B
58	75.9	≤6	4.66	63	24	C
59	1.8	≤6	1.69	43	10	B

$$(d_1+0.4)\times(d_2+0.4)\times(d_3+0.4)\times 0.52$$
$$=\text{volume of hypoechoic lesion in ml}$$
$$d_1\times d_2\times d_3\times 0.52$$
$$=\text{volume of whole prostate in ml}$$

For staging, the criteria published previously were used (Scardino *et al.*, 1989). A bulging, irregularity or obscuring of the prostatic capsular margin in the hypoechoic area was judged as indicating extracapsular extension. The seminal vesicles were assessed in all cases. When they appeared adherent to the prostate in association with a hypoechoic lesion at its base, or if they displayed posterior convexity, they were described as involved with tumour. Biopsies for staging purposes, such as seminal vesicle or extraprostatic tissue biopsy, were not obtained routinely; if they were, the biopsy result was not used in assessing TRUS stage for the purpose of this study.

PSA

PSA was measured in blood samples from all patients with the Tandem-R monoclonal immunoradiometric assay (normal 0–4 ng/ml) (Hybritech, Inc., San Diego, USA). To avoid false elevations, measurements were taken either before rectal manipulation or several weeks afterwards. The most recent value was used for all data analysis, but values were not used by the ultrasonographer in determining stage by TRUS (Table 3).

Pathology

The pre-operative biopsies were graded according to the Gleason system. A combined score was determined by adding the grades of the predominant 2 patterns. If more than 1 set of grades was described for multiple biopsies, the scores for that patient were averaged. We have found that biopsy grades often underestimate the grade of the final specimen (Narayan *et al.*, 1989); if the averaged scores did not result in a whole number, the average was therefore rounded upwards (this was necessary in only 7 patients). The prostate specimens after radical prostatectomy were placed in 10% formalin and sectioned into 3- to 5-mm slices after marking the surgical margin with black ink. No attempts were made to quantify the tumour mass exactly.

Pathological stages were assigned. Stage B tumours were those that did not extend outside the capsule (if identifiable), involve the surgical margins or invade the seminal vesicle. Invasion of the capsule without periprostatic adipose tissue involvement (extracapsular extension) was considered Stage B. Stage C tumours were those that extended into the periprostatic adipose tissue, involved the surgical margins or invaded the seminal vesicle. As our intent was to measure the accuracy of pre-operative staging of local disease, the lymph node status was not used in defining the pathological stage for analysis. Nonetheless, all patients in this series with lymph node involvement did have Stage C disease locally. Stage B disease was considered "contained" and Stage C disease was considered "uncontained".

Statistics

A true positive (TP) result indicated patients with uncontained disease in whom this was predicted; false positive (FP) indicated patients with contained disease in whom uncontained disease was predicted. In patients in whom contained disease was predicted, true negative (TN) and false negative (FN) indicated contained and uncontained disease respectively. Sensitivity was defined as TP/(TP+FN), or the percentage of patients with uncontained disease predicted as such; specificity was TN/(TN+FP), or the percentage of patients with contained disease predicted as such. Positive predictive value (PPV),TP/(TP+FP), was the likelihood of the disease being uncontained if it was so predicted; negative predictive value (NPV), TN/(TN+FN), was the likelihood of disease being contained if it was so predicted. Accuracy was defined as (TP+TN)/(TN+TP+FN+FP), or the percentage of accurate staging in all patients.

Results

Of the 48 patients, 11 had pathological Stage B tumours, all without lymph node involvement, and 37 had local Stage C disease, including 11 with microscopic lymph node metastases. Fourteen patients had seminal vesicle involvement, only 2 of whom did not also have positive margins or extracapsular extension.

Results of the prospective analysis of staging by TRUS in terms of extracapsular extension are shown in Table 4. In 4 patients extracapsular extension was predicted on only one side of the prostate but bilateral extracapsular disease was detected on pathological examination. One patient had unilateral extracapsular extension in the pathology specimen but had been predicted to have bilateral extracapsular disease. All 5 of these patients were considered to have TP predictions by TRUS. In all other cases categorised as TP the extent of disease predicted by TRUS correlated well with the pathological results.

Results of the prospective analysis of staging by TRUS in terms of seminal vesicle involvement are shown in Table 5. In 4 patients seminal vesicle

Table 4 Results of TRUS Staging Alone—Extracapsular Extension

	Pathological stage		
TRUS stage	*Contained*	*Uncontained*	*Total*
Contained	12	17	29
Uncontained	*1*	*18*	19
Total	13	35	

Sensitivity 51%. Specificity 92%. PPV 94%. NPV 41%. Accuracy 63%.

Table 5 Results of TRUS Staging Alone—Seminal Vesicle Involvement

	Pathological stage		
TRUS stage	*Contained*	*Uncontained*	*Total*
Contained	34	6	40
Uncontained	*0*	*8*	8
Total	34	14	

Sensitivity 57%. Specificity 100%. PPV 100% NPV 85%. Accuracy 88%

involvement was predicted to be unilateral but bilateral infiltration was found pathologically. One patient with unilateral involvement had been predicted to have bilateral disease. All 5 were considered to have TP predictions by TRUS. In the remaining cases of TP prediction the extent of disease was as predicted.

Results of the overall staging by TRUS are shown in Table 6. A TRUS that predicted uncontained disease at any site that was confirmed on pathological examination was considered to be TP. This resulted in the one patient with a FP TRUS for extracapsular extension being considered to have a TP prediction overall, as his involved seminal vesicles had been correctly predicted. A second patient with a FN prediction for extracapsular extension had a TP prediction for seminal vesicle involvement and was considered to have a TP prediction overall. A third patient had a TN prediction for extracapsular extension but a FN prediction for seminal vesicle involvement, so the overall prediction was FN. The results of overall TRUS staging were similar to the results of extracapsular staging, with a sensitivity of only 54% and overall accuracy of 65%. Eight of the 11 patients with lymph node metastases were correctly identified by TRUS as having uncontained disease.

PSA values in this group ranged from 1.1 to 85 ng/ml. In the 12 patients with more than 1 PSA measurement (excluding 1 stage A2 patient with marked decrease in PSA after transurethral resection of the prostate), the individual differences averaged 2.2 ng/ml, or 23% of the initial value. The subsequent analysis was not altered if the initial PSA, rather than the most recent, was used.

Table 6 Results of TRUS Staging Alone—All Sites

	Pathological stage		
TRUS stage	*Contained*	*Uncontained*	*Total*
Contained	11	17	28
Uncontained	*0*	*20*	20
Total	11	37	

Sensitivity 54%. Specificity 100%. PPV 100%. NPV 39%. Accuracy 65%.

Based on the PSA value, the combined grade of the initial biopsy and the results of sizing of the prostate gland and hypoechoic region by TRUS, an "expected" PSA was obtained. This value was computed as:

$$\begin{gathered}\text{K} \times \text{volume of hypoechoic region in ml} \\ + \\ 0.07\ \text{ng/ml} \times \text{volume of whole prostate in ml}\end{gathered}$$

where K is 2.1 ng/ml for tumours with the combined score of ≥ 7 and 4.2 ng/ml for tumours with the combined score of ≤ 6 (see Discussion section for explanation).

The expected PSA was then compared with the actual PSA. If the latter was less than or equal to the former (calculated to 2 significant digits), the patient was considered to have contained disease. Results of staging by this PSA formula are shown in Table 7.

Table 7 Results of PSA Formula Staging Alone

	Pathological stage		
PSA formula stage	*Contained*	*Uncontained*	*Total*
Contained	9	16	25
Uncontained	*2*	*21*	23
Total	11	37	

Sensitivity 57%. Specificity 82%. PPV 91%. NPV 36%. Accuracy 63%

The 11 patients with contained disease fell into 2 groups: Group I (9 patients) was TN by both TRUS and the PSA formula; Group II (2 patients) was TN by TRUS, but FP by PSA. The 37 patients with uncontained disease fell into 4 groups: Group III (6 patients) was FN by both TRUS and PSA, Group IV (10 patients) was TP by both TRUS and PSA, Group V (10 patients) was TP by TRUS but FN by PSA, and Group VI (11 patients) was FN by TRUS but TP by PSA.

A new staging method was created by combining the PSA formula and the TRUS results, so that a patient who tested positive for uncontained disease by *either* parameter was considered to have uncontained disease by the combined staging. Compared to TRUS alone, the outcome (Table 8) was an

Table 8 Result of Combined TRUS and PSA Formula Staging

TRUS and PSA formula stage	*Pathological stage*		
	Contained	*Uncontained*	*Total*
Contained	9 (Group I)	6 (Group III)	15
Uncontained	2 (Group II)	*31**	33
Total	11	37	

Sensitivity 84%. Specificity 82%. PPV 94% NPV 60%. Accuracy 83%.

*Includes Group IV (10), Group V (10) and Group VI (11).

improvement in sensitivity (84%), NPV (60%) and accuracy (83%), with minimal change in specificity (82%) and PPV (94%). All 11 patients with lymph node metastases were correctly identified as having uncontained disease by the combined staging. They fell evenly into the 3 groups that comprised the TP populations: 5 in Group IV, 3 in Group V and 3 in Group VI.

Analysis of some of the parameters from the combined staging is shown in Table 9. Each component was less predictive of stage than the combined method.

Discussion

As experience with treatment modalities for prostate cancer increases, we learn more about their appropriate application to different subsets of patients. Implicit in the goal of the best therapy for each individual patient is accurate pre-operative staging. TRUS is no doubt used routinely for staging in many centres, but our data show that comparing PSA values with a theoretical "expected" PSA may help to identify patients with Stage C disease who otherwise might have been staged as B by TRUS alone.

Several studies have noted the increased incidence of Stage C and D tumours if the PSA is elevated above 10 ng/ml (Table 2). This number is rather arbitrarily applied to all patients, without factoring in the size of the prostate, the size of the presumed tumour and the grade of the lesion, all of which will affect the degree of PSA elevation. Of the 13 patients upstaged by our formula (*i.e.* negative TRUS and positive PSA, or Groups II and VI), 8 (62%) had PSA values <10.0 ng/ml.

Stamey *et al.* (1989) found that PSA was elevated 3.5 ng/ml for every ml of tumour. This figure was derived from PSA levels as measured by the Pros-check polyclonal radioimmunoassay (Yang Laboratories, Bellvue, USA). Values obtained with the Yang kit are 1.4 to 1.9 times higher than those from the Hybritech kit that we used (Graves *et al.*, 1989). With 1.65 as an approximate correction factor, PSA was estimated to be elevated 2.1 ng/ml for each ml of tumour with a score of 7 or higher. We separated the tumours by Gleason combined score because of the inverse correlation between grade and PSA when adjusted for tumour volume (Partin *et al.*, 1990). While two-thirds of the patients in the study by Stamey *et al.* (1989) had a Gleason combined score of 7 or higher, only 21 of 48 patients (44%) in our group had biopsy scores of 7 or higher. We started therefore with 2.1 ng/ml per ml of tumour as a reasonable estimate for tumours of combined grade 7 or higher, and doubled the value to 4.2 ng/ml per ml of tumour for lower grades.

To estimate the amount of PSA elevation expected with non-hypoechoic tissue (*i.e.* whole prostate), we started with the calculated value of 0.3 ng/ml per ml of benign hyperplastic prostate tissue (Stamey *et al.*, 1989). This is equivalent to 0.18 ng/ml per ml with the Hybritech assay. We used a lower figure because the non-cancerous portions of the prostate presumably contained normal as well as hyperplastic tissue, the former

Table 9 Summary of Parameters of TRUS and PSA Formula Staging

Predictive of uncontained	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
Hypoechoic lesion ≥1.0 ml	89	27	80	43	75
Hypoechoic lesion ≥2.0 ml	68	82	93	43	71
Hypoechoic lesion ≥3 0 ml	43	91	94	32	54
Biopsy score ≥7	51	82	86	35	58
PSA ≥10 ng/ml	46	91	94	33	56
TRUS · +SV or +ECE*	54	100	100	39	65
PSA actual > PSA expected	57	82	91	36	63
Combined staging	84	82	94	60	83

*With seminal vesicle involvement or extracapsular extension

Table 10 Mean Biopsy Score, Size of Hypoechoic Lesion and PSA Values

Patient group	*TRUS stage*	*PSA formula stage*	*Combined stage*	*Biopsy score*	*Size of hypoechoic lesion (ml)*	*PSA (ng/ml)*
I	TN	TN	TN	5.0±1.1*	2.6±3.8	4.5±3.3
II	TN	FP	FP	6.0±1.0	0.9±0.1	7.7±2.0
III	FN	FN	FN	5.5±1.3	2.2±1.0	5.6±2.1
IV	TP	TP	TP	7.0±1.1	4.9±2.9	31.9±22.3
V	TP	FN	TP	6.3±1.0	7.2±8.0	7.3±5.5
VI	FN	TP	TP	6.5±1.7	2.0±1.1	20.4±21.7
IV+V+VI			TP	6.6±1.3	4.5±5.2	19.9±20.9
All				6.1±1.4	3.7±4.6	15.0±18.6

* ±SD.

contributing negligible PSA elevation. The figure of 0.07 ng/ml was chosen retrospectively as it represented the value at which the best correlation could be obtained. The appropriateness of this estimate was confirmed by evaluation of the TRUS and PSA measurements of 10 randomly chosen men with sonographically benign prostates (most with obstructive symptoms). In 8/10 cases the expected PSA (0.07 × prostate volume) was greater than or equal to the actual PSA. If we had used 0.18 instead of 0.07 as the estimate for the whole prostate, the PSA stage would have been changed from TP to FN in 10 patients from our series.

It is reasonable to hypothesise that a PSA value higher than expected for a given tumour might indicate a source of PSA not yet appreciated by the clinician. Local extracapsular extension not seen on TRUS or palpated on digital rectal examination, iso- or hyper-echoic tumours (not noted on TRUS as cancer) or silent metastases might all elevate PSA and represent a higher true stage than would otherwise be appreciated. Our formula helps to identify these patients with tumour extension not found on TRUS or rectal examination and quantifies the clinical impression that is made when the PSA is unusually elevated. If a patient's actual PSA is higher than might be expected, the clinician must be suspicious of spread of the lesion outside the prostate, even if the TRUS or rectal examination suggests that the tumour is completely contained.

In an effort to improve our staging method, we tried to identify factors that might have contributed to the erroneous staging of 8 patients (6 FN, 2 FP). An analysis of biopsy score, size of hypoechoic lesion and PSA is shown in Table 10. None of these factors was discriminating enough to indicate a deficiency in the staging.

We did note that 9 patients had biopsy results positive for cancer from a prostatic lobe where no lesion was identified on TRUS. Of these patients, 6 were predicted TP, 1 was FP and 1 FN. Re-analysis of the data, omitting these 9 patients, made no difference to the accuracy of the staging. In only 1 patient was biopsy of a hypoechoic lesion on TRUS benign (a second lesion was malignant); contained disease was correctly predicted.

In conclusion, we have devised a method for locally staging prostate cancer that combines TRUS with a formula based on PSA values, biopsy tumour grades and TRUS sizing—all data available preoperatively. We feel that staging information as derived from this method could be used in weighing the possible benefits of various therapeutic options for an individual patient. Although promising, it should be pointed out that this formula was devised retrospectively, and prospective investigation will be required to evaluate fully this addition to our staging methods.

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Mitomycin C and Aminoglutethimide in the Treatment of Metastatic Prostatic Cancer: a Phase II Study

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Summary—In a phase II study, 24 patients with metastatic prostatic cancer were treated with mitomycin C 15 mg/m^2 i.v. every 6 weeks, combined with aminoglutethimide 250 mg twice a day. A low dose of 37.5 mg cortisone acetate was supplied daily to compensate for adrenal cortical suppression. A partial reponse was demonstrated in 4 of 24 evaluable patients with bi-dimensionally measurable metastases. Stable disease occurred in 8 patients over a period of more than 6 months. Within the maximum cumulative dose limit of 2 mg/kg body weight mitomycin C, toxicity was observed in 21 cases, including 2 deaths due to treatment toxicity. The poor response rate and high toxicity suggest that the addition of aminoglutethimide does not enhance the effect of mitomycin C in these patients.

Mitomycin C has been available for over 30 years and can provide a partial response rate of 30% in patients with hormone-resistant metastatic prostatic carcinoma (Baker and Vaitkevius, 1979; Jones *et al.*, 1986; Veronesi *et al.*, 1989).

Aminoglutethimide, a derivative of glutarimide, inhibits adrenal production of aldosterone, cortisol and androgens and can produce a subjective response of up to 60% in these patients (Dexter *et al.*, 1967; Robinson *et al.*, 1974; Sanford *et al.*, 1976; Smith *et al.*, 1978; Robinson, 1980; Rostom *et al.*, 1982; Drago *et al.*, 1984; Labrie *et al.*, 1989).

According to the EORTC Genito-urinary Group criteria, only measurable lesions should be used to determine objective response in phase II studies. Similarly, serum markers such as acid and alkaline phosphatases cannot be used because they do not correlate sufficiently with the course of the disease. The criteria for objective response in this study were bi-dimensionally measurable lesions. The quality of life was also estimated by means of a questionnaire.

Patients and Methods

Patients of any age were admitted to the study provided that their estimated survival was more than 3 months, that they had a performance status not less than WHO 3, that they had a white blood cell count of more than 3×10^9/l, a platelet count of more than 100×10^9/l, and a serum creatinine of 120 μmol/l or less. Radiotherapy to a measurable lesion excluded that lesion as a parameter. All patients had to have a castration level of serum testosterone. Patients pre-treated with 1 of the trial drugs were excluded from this study, as were patients who had another malignancy, except for a well treated non-melanoma skin cancer.

Between December 1986 and October 1989 a total of 24 patients entered the study. The mean age was 68 years (range 54–83). Of these, 2 patients had Grade 1 tumours, 9 had Grade 2 and 12 had Grade 3 tumours. In 1 patient the grade could not be assessed. Previous treatments for prostatic cancer are summarised in Table 1.

All patients had received previous hormonal treatment: 19 patients underwent orchiectomy and 5 received an LHRH analogue. In addition, 2 patients had received estramustine, 7 had received cyproterone acetate, and 2 had used both. These medications were discontinued in all of these 9 patients. The distribution of indicator lesions is given in Table 2.

Every 6 weeks the patients visited the out-patient department to receive 15 mg/m^2 body surface

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Table 1 Previous Treatment

Therapy	*No of patients*
Castration	19
LHRH analogue	5
TUR prostate	11
Radical prostatectomy	3
Radiotherapy to prostate	6
Radiotherapy to metastasis	4
Estramustine phosphate	2
Cyproterone acetate	7

Table 2 Indicator Lesions

Site of lesion	*No. of patients*
Lytic bone metastasis	2
Abdominal lymph nodes	14
Palpable subcutaneous metastasis	3
Liver metastasis	2
Lung metastasis	2
Prostate	1

Table 3 Toxicity

	WHO performance status				
Side effects	*0*	*1*	*2*	*3*	*4*
Toxicity related to mitomycin C					
Thrombocytopenia	·	·	1	4	·
Leucopenia	·	4	3	3	·
Anaemia	5	5	5	4	2
Loss of hair	1	2	·	·	·
Interstitial pneumonia	·	·	·	·	1
Cardiomyopathy	1	·	·	·	1
Fever	1	3	2	·	·
Stomatitis	2	2	·	·	·
Nausea, vomiting	7	·	·	·	·
Toxicity related to aminoglutethimide					
Exanthema	·	·	2	1	·
Headache	·	2	·	·	·
Nausea, vomiting	·	·	3	·	·
Loss of appetite	·	10	4	·	·
Lethargy	·	·	4	·	
Hypotension	·	2	1	·	·
Hypothyroidism	1	1	·	·	·
Alveolitis	·	·	·	·	1
Bleeding peptic ulcer	·	·	·	·	1

Table 4 Results

Response	*No. of patients*
Complete remission	0
Partial response	4
No change	8
Progressive disease	9
Early death	3

mitomycin C intravenously to a maximum dose of 2 mg/kg body weight. The median number of cycles was 3 (mean 3.62, range 1–7). Aminoglutethimide was given in doses of 250 mg twice a day. Cortisone acetate was supplied in low doses of 25 mg in the morning and 12.5 mg in the afternoon.

Results

Three patients died before the first evaluation after 2 cycles (1 from malignant disease, 1 from a bleeding gastric ulcer and 1 from cardiac insufficiency). These 3 patients had a WHO performance score of 3 at the start of treatment and they died within 10 weeks of the start of therapy without further evaluation. Toxicity was observed in 21 patients (Table 3).

In 1 patient lethal lung and kidney damage was observed as a result of mitomycin C toxicity. Another patient died of alveolitis, a rare side effect of aminoglutethimide.

After discontinuing aminoglutethimide, nausea, loss of appetite and headache disappeared completely in 3 patients. Only 3 of 24 patients (12.5%) were free of side effects.

The response rate is shown in Table 4. No complete responses were observed. Of the 4 patients with a partial response (PR), 2 had a decrease in size of metastatic para-aortic lymph nodes, 1 had a decrease in prostatic volume of more than 50% and 1 showed sclerosis of an osteolytic bone metastasis. Of these 4 patients, 2 suffered from severe treatment toxicity. Only 1 is still alive more than 1 year after the start of treatment. His serum PSA level has dropped from 141 to 6.9 µg/l. The patient with the partial response of the prostate died after 12 months as a result of cardiac failure.

The average survival of 8 patients with no change (NC) was 58 weeks (range 38–88) (Fig. 1). Patients with progressive disease showed progression 6 to 26 weeks after the start of treatment (average 16 weeks). The progression-free interval is summarised in Figure 2.

The pain score was improved in 7 patients after 1 course and in 3 patients after 2 courses. The WHO quality of life score improved in 5 patients after 1 course.

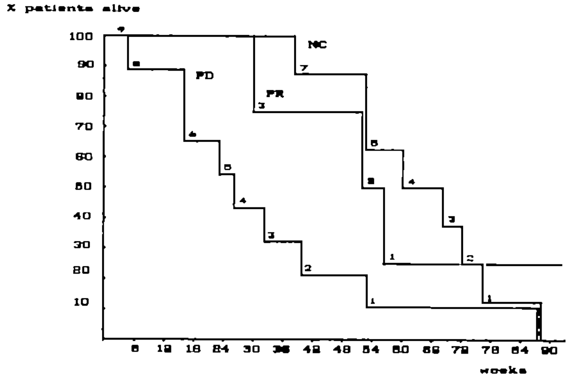

Fig. 1 Survival of patients according to response NC = no change; PR = partial response; PD = progressive disease. Arabic numbers indicate the number of patients at risk.

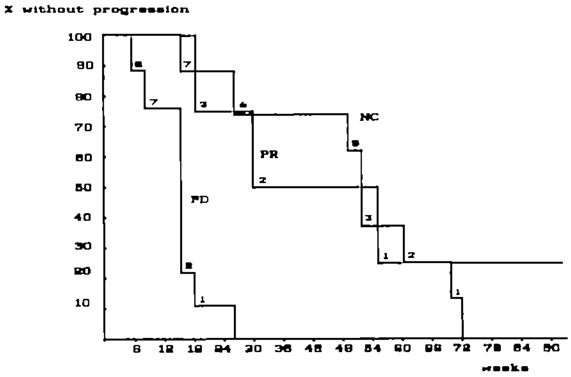

Fig. 2 Progression of disease according to response. NC = no change; PR = partial response; PD = progressive disease. Arabic numbers indicate the number of patients at risk of progression

Discussion

This phase II study revealed moderate anti-tumour activity in patients with progressive measurable metastatic disease, with a 17% partial response rate (4/24 patients).

The mean duration of partial responses was 40 weeks, which is longer than the 24 weeks reported by Jones *et al.* (1986) and the 20 weeks reported by Veronesi *et al.* (1989). This may be an adjuvant effect of aminoglutethimide or perhaps the effect of the low dose corticosteroids which were given, but the figures are too small to be conclusive.

Combination therapy with mitomycin C and aminoglutethimide does not seem to be effective in improving the quality of life (only 5/21 patients' quality of life improved) or in relieving pain.

In patients such as these it will always be difficult to discriminate between progression of disease and the toxic side effects of certain drugs, but side effects were observed frequently. Most of these were mild and bearable. However, 2 of the 4 patients with a partial response died from treatment toxicity. Another patient showed only mild cardiotoxicity—pericarditis which subsided after stopping treatment.

Mitomycin C was discontinued in 6 patients after several courses because of severe haematological disorders. Of a total of 87 mitomycin C treatments, 6 were postponed because of leucopenia in 3 patients. In 4 instances the therapy was stopped because of severe thrombocytopenia or pancytopenia. Blood transfusions were given to 18 of the 24 patients.

Since this study resulted in 1 early death from cancer, 2 definite toxic deaths, 2 other possible toxic deaths, only 3 patients without side effects, no complete responses and only 4 of 24 partial remissions, it was concluded that the addition of aminoglutethimide to mitomycin C was of no benefit. As all of the early deaths occurred in patients with a WHO performance status exceeding 2, it seems justified to exclude these patients from such treatment.

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High Resolution Ultrasonography in the Diagnosis of Simple Intratesticular Cysts

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Summary—Simple intratesticular cysts are a rare condition. High resolution sonography permits unequivocal sonographic differentiation between intratesticular cysts and neoplastic lesions with a cystic appearance, so that conservative treatment seems justified. Seventeen patients with sonographically diagnosed intraparenchymal testicular cysts were followed up for an average of 29 months. No increase in size or change in echo pattern was found and surgical intervention was therefore not indicated.

Simple intratesticular cysts are extremely rare, but their incidence appears to be increasing with the more frequent use of testicular sonography (Takihara *et al.*, 1982; Rifkin and Jacobs, 1983; Kratzik *et al.*, 1988). In the majority of cases described in the literature, the cyst was excised after inguinal exposure of the testis; since malignancy could not be excluded, however, some patients underwent orchiectomy.

Scrotal sonography using high frequency transducers (scan head frequency 7.5–10 MHz) is a sensitive method of establishing the site and morphology of space-occupying lesions. Goli *et al.* (1980) and Turner *et al.* (1977) quoted an incidence of 1 to 3.5% for benign lesions in the testis, but more recent studies, using sonographic diagnostic procedures, have reported an incidence of 17 to 58% (Belville *et al.*, 1982; Chang *et al.*, 1987; Haas *et al.*, 1987). Sonography is of great value in the early recognition of such lesions. Pathological abnormalities of the scrotal contents may be diagnosed by ultrasonography with a sensitivity of 98.5% (Rifkin *et al.*, 1985; Kaiper, 1989) and a diagnostic accuracy of 88% (Willscher *et al.*, 1983).

Intratesticular lesions with a cystic appearance are a rare sonographic finding and the majority are found to be epidermoid cysts. Their sonographic appearance usually differs clearly from that of pure intraparenchymal testicular cysts. Since the simple benign intratesticular cyst presents typical cystic characteristics when investigated by high resolution sonography, an accurate diagnosis can be made and conservative treatment thus seems appropriate.

Patients and Methods

Seventeen patients with sonographically diagnosed intratesticular cysts were evaluated retrospectively. The mean observation period was 29.3 months (range 1–108). The patients' mean age was 40.3 years (range 19–77). None of the cysts was detectable by physical examination. In every case the diagnosis was established accidentally during routine testicular sonography for other reasons and none of the patients had clinical symptoms related directly to these cysts. Table 1 lists the indications for testicular sonography and Table 2 shows the

Table 1 Indications for Testicular Sonography

	No
Palpable space-occupying lesion (epididymal cyst or fibroma of the tunica)	8
Trauma	1
Status post contralateral tumour	2
Routine sonography (search for focus)	2
Hydrocele	4
Total	17

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Table 2 Morphological Criteria of Intratesticular Cysts*

	No.
Location	
Peripheral	6
Central	11
Side	
Right	6
Left	7
Bilateral	4
Solitary	13

*Mean size 9 mm (range 3–35).

morphological criteria. Cysts related to the tunica albuginea were not included in this study. Chest radiography, sonography of the retroperitoneal space and testicular tumour markers (β-HCG, AFP) were performed routinely when the diagnosis was established in order to exclude malignant testicular tumours. Sonography was repeated at 3-monthly intervals during the first 2 years and then twice a year; it was performed with a high frequency transducer (7.5–10 MHz) (Ultramark 4, Squibb Medical Systems).

Results

β-HCG and AFP were in the normal range in every case. All 17 patients remained untreated and were followed up at regular intervals. None of the cysts increased in size or showed any morphological change. The typical echo pattern displayed all of the sonographic characteristics associated with cystic lesions in other organs. There was a roundish anechoic lesion with enhanced posterior sound transmission (Fig. 1). Larger cysts also showed the characteristic "lateral shadow" phenomenon (Fig. 2). High magnification revealed a more echogenic rim around the cysts due to compression of the testicular parenchyma. In every case this rim had a homogeneous pattern. There was no evidence of testicular tumour.

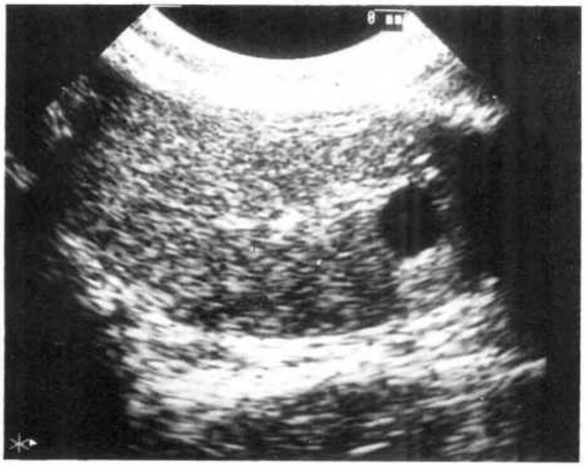

Fig. 1 Specimen assessed by 10 MHz transducer: intratesticular cyst with typical cyst characteristics.

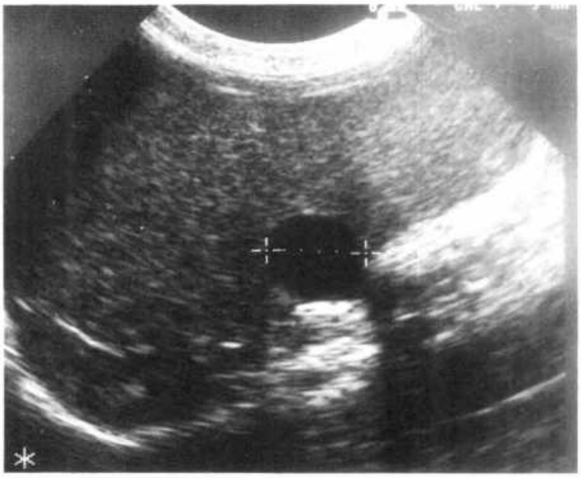

Fig. 2 Non-palpable intratesticular cyst 9 mm in diameter; typical lateral shadow phenomenon. (10 MHz transducer).

Discussion

Since the incidence of benign intratesticular lesions is higher than originally assumed (Haas *et al.*, 1987), the main value of sonography lies in its ability to detect these lesions and thus avoid surgical intervention. The sensitivity of sonography in recognising pathological intratesticular changes is approximately 90% (Nachtsheim *et al.*, 1983) and cystic lesions can be diagnosed with high frequency transducers with an even higher degree of accuracy (Takihara *et al.*, 1982; Rifkin and Jacobs, 1983).

Simple anechoic cysts within the testicular parenchyma must be distinguished from other cyst-like space-occupying lesions, such as epidermoid cysts. Cystic areas may also be found in tumours and intratesticular abscesses or haematomas sometimes display cystic characteristics. Moreover, an oblique section of a large intratesticular vessel may mimic a cystic lesion.

The epidermoid cyst presents a sonographic image similar to that of the simple intratesticular cyst, although it appears more like a roundish, well defined, homogeneous space-occupying lesion. The content of epidermoid cysts is more echo-rich because of keratin deposits; these lesions are surrounded by a ring of higher echo density which is more echogenic than that seen in pure cysts and

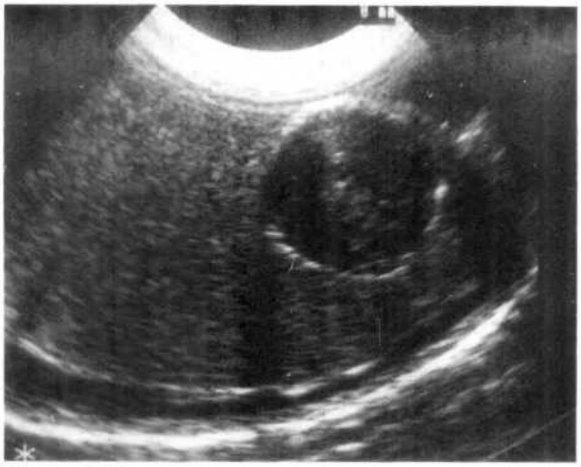

Fig. 3 Epidermoid cyst of testis. Solitary encapsulated lesion with echo-rich content and lack of dorsal acoustic enhancement. (10 MHz transducer).

the dorsal acoustic enhancement, typical of simple cysts, is missing (Fig. 3).

While a testicular tumour often produces echo-poor focal or diffuse changes in the usual completely homogeneous echo pattern, necrosis or haematoma in a tumour may exhibit an echo-poor or anechoic cystic character (Fig. 4). Teratomas in particular frequently show sonographic areas with a cyst-like appearance (Leopold, 1981). Nevertheless, clear sonographic differentiation from benign intratesticular cysts is possible, since no change in the testicular architecture—apart from the cyst itself and possible compression of the surrounding testicular tissue—is observed in the latter case.

The increasing use of sonography has revealed a higher incidence of simple intratesticular cysts (Rifkin and Jacobs, 1983; Chang *et al.*, 1987; Hamm *et al.*, 1988; Kratzik *et al.*, 1988; Kratzik *et al.*, 1990) than that reported in earlier publications (Schmidt, 1966; Tosi and Richardson, 1975; Takihara *et al.*, 1982). Morphologically, the cysts are filled with a clear serous liquid with no cellular elements and lined by cylindrical epithelium.

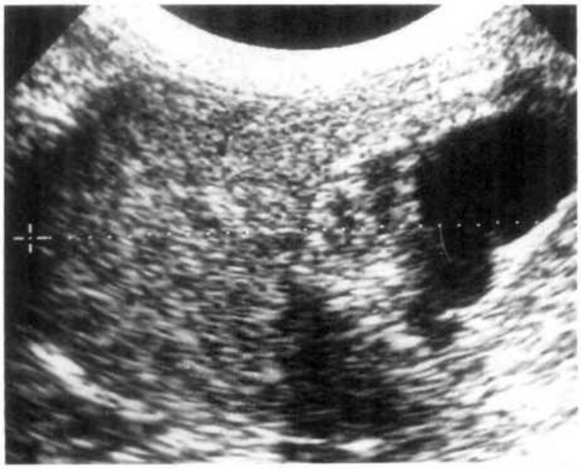

Fig. 4 Cystic lesion within inhomogeneous testicular mass (teratoma). (10 MHz transducer).

Various pathogenetic theories have been put forward. Congenital development arising from remnants of the müllerian or the wolffian duct (Jenkins and Denning, 1935) has been suggested, since such cysts have been reported in children (Schmidt, 1966). A post-traumatic origin cannot be excluded (Takihara *et al.*, 1982).

In all cases of intratesticular cysts reported in the literature where pre-operative sonography had been performed, the sonographic diagnosis was confirmed in the surgical specimen (Leopold, 1981; Takihara *et al.*, 1982; Kratzik *et al.*, 1990). We feel that conservative management is justified when the sonographic diagnosis is unequivocal. Prerequisites are accurate diagnostic clarification and exclusion of malignant intratesticular lesions. In addition, sonographic follow-up at regular intervals is essential. Surgical exploration is indicated if there is any change in the morphological image.

Sonography permits a clear differentiation to be made between neoplastic cystic lesions and non-neoplastic cysts, so that conservative management of simple intratesticular cysts is justified and the patient can be spared unnecessary surgical intervention.

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PAEDIATRIC UROLOGY

Total Nephrectomy in Children: A Clinicopathological Review

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Summary—The records of 85 children undergoing total nephrectomy have been reviewed. Diagnoses ranged between pyelonephritis (37 patients), renal tumours (25), renal dysplasia and multicystic kidney (16), obstructive uropathy (6) and renal vein thrombosis (1). In the pyelonephritic group a contributory ipsilateral abnormality was demonstrated in 36 of the 37 children. Vesicoureteric reflux (VUR) was the most common abnormality in this cohort and was usually of a severe grade. Calculus disease was present in 9 patients, only 1 of whom had VUR. Of the remaining 7 patients with pyelonephritis, 6 had evidence of obstruction to the upper tracts. Calculus disease poses a more severe threat to the childhood kidney than the well known risk factors of vesicoureteric reflux and obstructive uropathy.

In spite of a move towards more conservative surgery (Whitaker, 1988), total nephrectomy remains an important option in the treatment of congenital and acquired diseases of childhood. Review of the literature reveals few reports on the indications for nephrectomy in this age group (Birken and Crooks, 1981; McAnena and Kelly, 1985). We have therefore reviewed our experience of the indications for nephrectomy in children and considered the clinical, pathological and radiological features of patients undergoing nephrectomy as a result of end-stage pyelonephritis.

Patients and Methods

The clinical notes, X-rays and pathological slides of a consecutive series of 95 children undergoing total nephrectomy during a 20-year period between 1969 and 1989 were reviewed. Adequate records were not available for 10 patients, leaving 85 patients suitable for evaluation. In all patients the diagnosis was confirmed histologically. Of those children undergoing nephrectomy for non-neoplastic disease, all underwent intravenous urography (IVU), 48 (80%) underwent micturating cystography (MCU) and 36 (60%) had pre-operative isotope renography. In the cohort of 37 patients with a final diagnosis of pyelonephritis, 35 (95%) had pre-operative micturating cystography and 23 (62%) had isotope renography. VUR was graded according to the classification of Smellie and Normand (1975).

Results

During the study period the most common indication for nephrectomy was chronic pyelonephritis (37 patients). Other indications were renal tumours (25), renal dysplasia and multicystic kidney (16), obstructive uropathy (6) and renal vein thrombosis (1) (Fig. 1). In one patient, the nephrectomy was iatrogenic in origin and was included in the obstructive group. The mean age of those undergoing nephrectomy for non-neoplastic disease was 6.2 years (range 1 day–14.2 years). In this group the male:female ratio was 1.9:1 and the right kidney was removed in 29 patients, the left in 31. A breakdown of these data for each underlying condition is provided in Table 1. The clinical details

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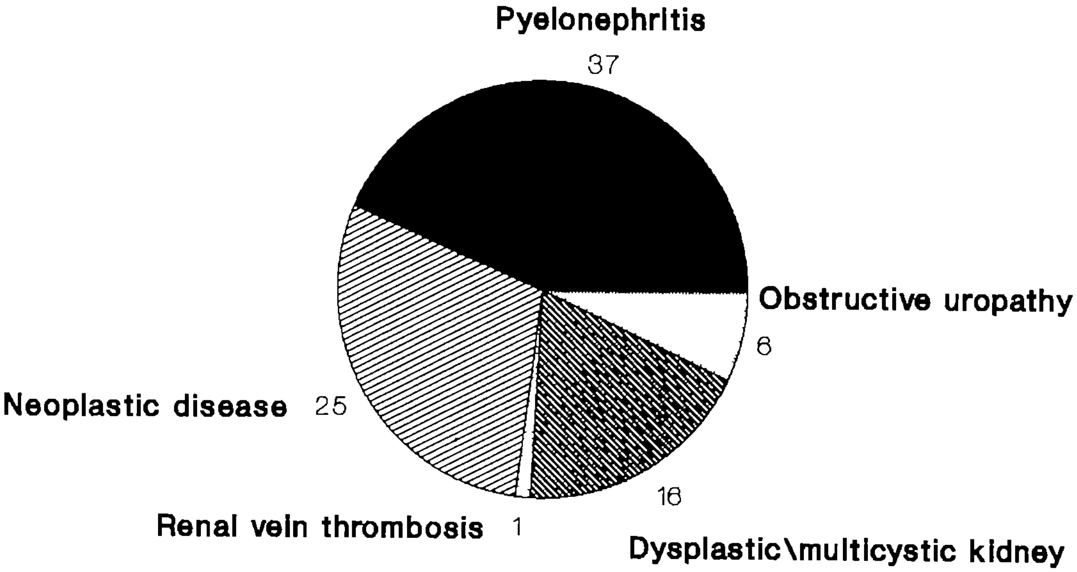

Fig. 1 Indications for nephrectomy in 85 children.

Table 1 Clinical Details of Patients with Non-neoplastic Disease

Pathology (no of patients)	*Mean age (years) (range)*	*Male female ratio*	*Side (R. L)*
Pyelonephritis (37)	8 3 (1 9–14.2)	19·18	20:17
Dysplasia/MCK (16)	1.8 (1 day–14.2 yrs)	14:2	5.11
Obstruction (6)	5.9 (4 0–13.7)	5:1	5·1
RVT (1)	1 5	1 0	0:1

MCK = multicystic kidney.
RVT = renal vein thrombosis

of those undergoing nephrectomy for non- or poorly-functioning kidney secondary to chronic pyelonephritis will be considered in greater detail.

In the pyelonephritic group there was an equal sex distribution. The mean age at nephrectomy was 8.3 years (range 1.9–14.2). The right kidney was involved in 20 patients, the left in 17. Associated ipsilateral abnormalities are shown in Figure 2. Of the 35 patients to have MCU, 24 had VUR, mostly severe (67% grade IV, 21% grade III). Non-calculus obstruction of the upper tract was demonstrated in 5 patients, 4 at the pelviureteric junction (PUJ) and 1 at the vesicoureteric junction. Of these, 1 patient had co-existing PUJ obstruction and reflux. A total of 9 patients with end-stage pyelonephritis had associated calculus disease and in all patients stones were of mixed infective type. All of this group underwent MCU but only 1 child was found to have coexisting VUR. Stones were confined to the pelvicaliceal system in 4 patients, solely ureteric in 2 and both pelvicaliceal and ureteric in 2.

In patients with end-stage pyelonephritis, contralateral abnormalities were found in 10 patients (VUR 7, stones 2 and renal scar 1). The nephrectomy was performed as a primary procedure in 23 patients (62%). Previous surgical interventions in the other 14 patients are listed in Table 2.

Discussion

Comparison of the present series with that published by McAnena and Kelly (1985) is difficult, as we have chosen to classify by histological diagnosis and not by aetiological factors. However, the

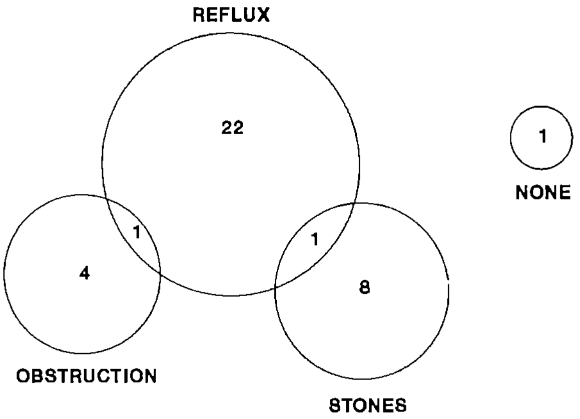

Fig. 2 Contributary ipsilateral pathology in 37 end-stage pyelonephritic kidneys.

Table 2 Previous Surgical Interventions

Surgical procedure	*No. of patients*
None	23
Ureteric reimplant	5
Open stone surgery	5
Pyeloplasty	1
Pyeloplasty/reimplant	1
Re-implant/open stone surgery	1
Resection of bladder neck (neurogenic bladder)	1

incidence of neoplastic disease in the present series is very much much higher (29%) than that seen by these authors (9%). Similarly, the incidence of dysplastic/multicystic kidneys was higher in this series (19 *versus* 6%). The reasons for these differences are unclear but may reflect a difference in patient population or the management of poorly functioning kidneys due to VUR or obstruction.

Ransley and Risdon (1978) suggested that pyelonephritis in childhood, in the absence of obstruction, was almost always a consequence of vesicoureteric reflux. Furthermore, Smellie and Normand (1975) stated that recurrent urinary tract infection in the absence of reflux and obstruction carried a good prognosis for renal function. Our results confirm these statements but underline the importance of calculus disease in the development of end-stage pyelonephritis in children.

As would be expected, children with pyelonephritis tended to be older than those with dysplastic or multicystic kidneys in the current series (Table 1). Those patients with end-stage reflux nephropathy tended to have more severe grades of reflux (87% grade III or IV VUR). This is in keeping with the correlation between grade of reflux and severity of scarring noted by other groups (Lenighan *et al.*, 1976; Winter *et al.*, 1983; Steinhardt, 1985). This observation is also reassuring as it confirms that few kidneys were lost by adopting a conservative management policy in milder grades of reflux.

A total of 9 patients with pyelonephritis had associated calculus disease (11% of total nephrectomies). This figure compares with 16% of total nephrectomies performed for stone disease in the paediatric series (McAnena and Kelly, 1985) and 6% for a large, mainly adult series (Schiff and Glazier, 1977). All of our patients with stone disease underwent MCU but reflux was documented in only 1 patient (11%). This figure is similar to the 8% incidence of reflux found in a series of childhood stones recently reported from this centre (Roberts and Atwell, 1989). The senior author (J.D.A.) has managed 60 children with stone disease over this period, total nephrectomy being necessary in 9 (15%). This rate contrasts markedly with the low nephrectomy rate seen in the surgical management of reflux over the same period (8%).

One patient, who underwent full investigation, had no obvious contributory cause for the development of pyelonephritis. The pathogenesis of progressive renal scarring in the absence of reflux, obstruction and stones is not clear. VUR in infancy or childhood which had resolved spontaneously would seem to be the most likely explanation. The demonstration of significant scarring without obvious cause is, however, well recognised. Winter *et al.* (1983) reported a series of 37 children with renal scarring in which 15 patients had negative MCUs—13 of these patients had repeat negative studies. Roberts *et al.* (1985) produced chronic pyelonephritis in a monkey with normal upper tracts after instillation of P-fimbriated *Escherichia coli* into the bladder. However, a recent study demonstrated that this organism was not commonly isolated in those children with renal scarring (Lomberg *et al.*, 1989). Clearly further studies are necessary.

Nephrectomy was the primary procedure in 23 patients, confirming that urinary tract infection in childhood often presents late with severe renal damage. The figure of 14 patients requiring nephrectomy after a previous intervention may seem disappointing. However, many patients who are candidates for total nephrectomy have bilateral upper tract abnormalities. There is therefore a reluctance to perform immediate total nephrectomy without a trial of more conservative surgery in an attempt to preserve renal tissue (Birken and Crooks, 1981). Other authors have suggested that when such poorly functioning kidneys are being evaluated, they should be assessed as if solitary (Birken and Crooks, 1981; Duckett, 1981). We agree with this view. This philosophy is further illustrated by the senior author's policy in managing bilateral VUR where 1 kidney is poorly functioning. The better functioning renal unit is surgically treated and the patient monitored for 12 months. If the patient's VUR remains corrected on the better side, with no further deterioration in that renal unit, a second-stage contralateral nephrectomy is performed.

This review confirms the threat posed by calculus disease to the kidney in childhood. Furthermore, it is clear that many children present late in the natural history of pyelonephritis, with end-stage kidneys. However, with improved awareness of the necessity to investigate children for septic episodes, there is hope that these children will present earlier in the disease course. This in turn may allow their management with more conservative surgery and a reduction in nephrectomy rates (McAnena and Kelly, 1985). In addition, the impact of the newer, less invasive means of treating stones in this age group is awaited.

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The Role of Tissue Expanders in Vaginoplasty for Congenital Malformations of the Vagina

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Summary—There are many techniques of vaginoplasty in congenital malformations of the vagina, all of which involve the use of labial and perineal skin flaps. The results are not uniformly satisfactory because of delayed stenosis in many patients. To avoid this complication, we have used labial expansion with tissue expanders to obtain an elastic and sufficiently large skin flap. We recommend this technique in patients with the adrenogenital syndrome associated with varying degrees of virilisation and in other intersex anomalies.

In the female adrenogenital syndrome, genitoplasty in infancy is an accepted concept (Fortunoff *et al.*, 1964; Sharp *et al.*, 1967; Hendren and Donahoe, 1980). However, vaginoplasty in infancy or early childhood is still controversial (Gonzalez and Fernandes, 1990). As a result of varying degrees of virilisation, the vagina is usually inserted in the urogenital sinus close to the external sphincter. In low insertion, vaginoplasty is usually performed with a cutback and placement of a perineal-based skin flap. In high insertion, however, the perineal vaginal pull through technique is used (Hendren and Donahoe, 1980). These techniques all require vaginal dilatation to be performed throughout infancy and childhood. Recent reports indicate that vaginal stenosis occurs frequently in adolescence (Gearhart *et al.*, 1992). Thus we recommend that vaginal reconstruction be deferred until puberty and that tissue expanders be used to obtain a large, well vascularised flap in order to perform an adequate, stenosis-free vaginoplasty (Lilford *et al.*, 1988). The selection of tissue expanders and the technique of vaginoplasty are described.

Patients and Methods

We have treated 2 female patients with the adrenogenital syndrome. The first (K.P., aged 12 years), with low insertion of the vagina, had undergone 2 vaginoplasty procedures (conventional technique) in infancy and childhood, but developed vaginal stenosis 10 years after surgery. The second patient (R.M., aged 14 years) had undergone vaginoplasty at 3 years of age and this had resulted in stenosis. She had high insertion of the vagina, close to the sphincter, and had started menstruation at the time of her vaginoplasty using a tissue expander.

Selection of tissue expanders

Prior to the selection of an appropriate expander, cystourethroscopy revealed the length of the defect from the vaginal cavity to the perineum to be approximately 5 cm. To create a flap measuring 5 to 6 cm an expander with a capacity of 250 ml was needed. In our patient a 250 ml expander provided a flap 10 cm long and 8 cm wide, with a 4 cm projection. An expander with a remote injection port is recommended to prevent accidental damage to the expander during filling (Table).

Placement of tissue expander and injection port

Under general anaesthesia a right inguinal incision was made and a labial pocket created to accommodate the 250 ml expander, which was placed flat without buckling in order to prevent extrusion during expansion. The remote port was placed in a deep subcutaneous pocket outside the pubic hairline while retaining its palpability.

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Table Guidelines for Selection of Tissue Expander

Criteria for size and number of expanders	Location and size of defect and donor site
Length of advancement of flap	Half of the length of expanded flap
Type of expander valve	Self-contained in the expander (Disadvantage: may puncture during inflation)
Remote valve	Needs dissection for placement. Avoids damage to expander during inflation
Incision for placement of expander	Remote site (prevents stress on suture line)
Size of pocket	1 cm larger than expander base

Inflation of the expander

The expander was filled 2 weeks after placement. At weekly intervals a 20 ml syringe was connected to a 25 gauge needle with extension tubing and normal saline was injected through the remote port. The volume of saline used on each occasion depended on the patient's tolerance of the discomfort; in all, 220 ml were injected over a 6-week period. In the seventh week vaginoplasty was performed.

Vaginoplasty

Bowel preparation was carried out the day before surgery with enemas and antibiotics. The patient was placed in the lithotomy position under general anaesthesia and a Fogarty balloon catheter was placed in the vagina through the common ostium. A 16 F urethral catheter was placed in the bladder and a U-shaped flap measuring 2 × 3 cm was raised from the midline perineal skin. With perineal dissection a space was created and the vaginal wall was identified by feeling the Fogarty balloon. The vaginal connection to the urethra was divided posteriorly close to its insertion but leaving a 0.5 cm margin. The Fogarty catheter was removed and transection of the anterior wall of the vagina was completed, avoiding injury to the urethra. The opening in the urethra was closed with 5/0 polyglycolic sutures in 2 layers and the vaginal ostium was held with stay sutures. The vaginal wall was then separated from the undersurface of the urethra minimally. An adequate perineal cavity was further developed by dividing the medial fibres of the surrounding levator ani muscles on either side. Further mobilisation of the vaginal ostium was not attempted, but the ostium was incised anteriorly and laterally to enlarge the opening. The gap between the vagina and the perineum measured 5 cm. A 10 × 8 cm skin flap was raised by incising the expanded labia. The implant was taken out, together with its remote port, preserving the newly developed vascularised sheath around the expander. The labial skin flap was rotated into the newly created perineal space to permit attachment of the skin edges and the vaginal ostium with 2/0 polyglycolic interrupted sutures (Fig. 1). The flap was approximated circumferentially, leaving a 1 cm triangular gap posteriorly. This was allowed to epithelialise. Distally, however, the U-shaped per-

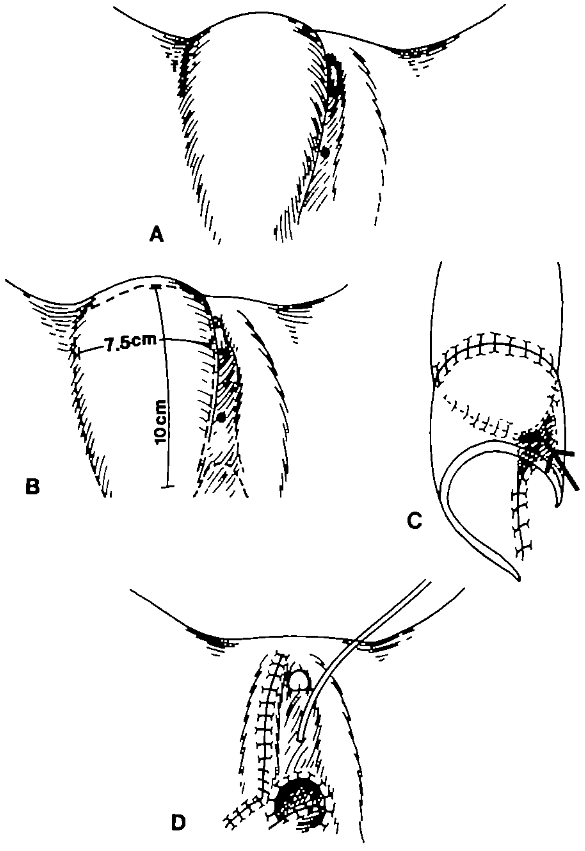

Fig. 1 (A) Labial pocket is created for placement of tissue expander. (B) Skin flap 8 × 10 cm is raised along with its vascular sheath. (C) The flap is rotated medially into the perineal space to be anastomosed to the native vaginal ostium cirumferentially, except for a 1 cm area posteriorly (D) Distally, the perineal U-shaped flap is stitched to the labial flap.

ineal flap was brought into the perineal space to approximate to the edges of the rotated labial flap. The other raw areas were covered by anastomosis of the adjacent skin edges to complete the vaginal ostium. The vaginal cavity was packed with 2.5 cm wide ribbon gauze in a latex glove, which was then placed in the vaginal cavity. The pack was removed on the third post-operative day rather than the fifth day because of the onset of menstruation. The urethral catheter was removed on the seventh post-operative day. Vaginal dilatation began 10 days after the repair and continued once a day for 3 weeks, and then 3 times a week for a further 6 weeks. The excess skin on the anterior lip of the vagina was fashioned into labia minora 3 months later.

Results

K.P., who had undergone 2 previous vaginoplasty procedures, developed recurrent stenosis 8 months after the recent repair and will require tissue expanders to achieve a satisfactory result. R.M. has a satisfactory vaginoplasty with excellent cosmetic and functional results and does not require dilatation 5 months post-operatively. Despite a large clitoris (Fig. 2) she does not wish any modifications to be made.

Discussion

The various techniques of vaginoplasty described in the literature use skin flaps raised from the perineal, lateral labial and preputial flaps (Fortunoff *et al*., 1964; Hendren and Donahoe, 1980). In spite of prolonged dilatations, reports suggest that vaginal stenosis is frequent in later years (Gearhart *et al*., 1992). In our 9 patients, aged between 6 months and 14 years, there have been no untoward effects due to the confluence of vagina and urethra and in 2 patients the menstrual fluid passes through the urogenital sinus. After satisfactory genitoplasty in infancy, the parents of our younger patients have decided to wait until later childhood or puberty for vaginoplasty. Depending on the size of flaps needed, multiple expanders may be used. However, labial placement of more than one tissue expander poses the problem of friction between the 2 labia, leading to chafing of the skin (Lilford *et al*., 1988). Youngsters may object to the disfigurement created by 2 expanders.

In congenital absence of the vagina, vaginoplasty can be performed with the fetal amnion membrane applied to the vaginal mould, which is placed in the 4 to 5 cm space created for the new vagina (Dhall, 1984). The AIDS epidemic, however, makes this approach unacceptable. Thus, we recommend the use of a tissue expander to create a large labial skin flap so that an adequate vagina can be formed which requires little or no dilatation. In patients with vaginal atresia and males who are to be assigned a female gender, we propose using expanded skin flaps and large bowel to create a neovagina and provide an excellent functional and cosmetic result.

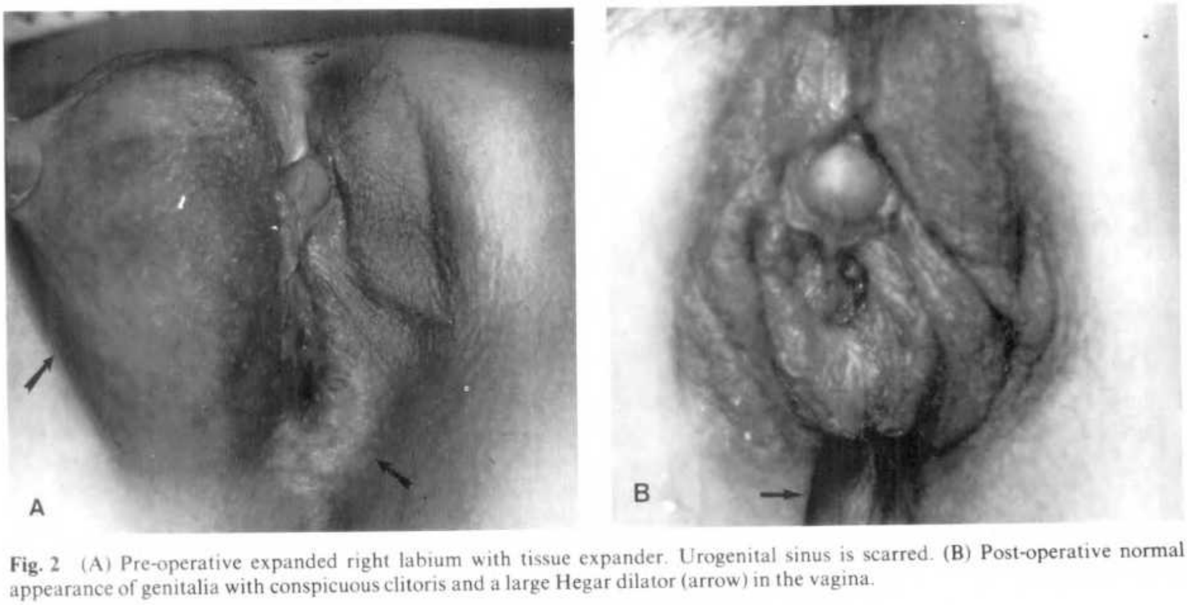

Fig. 2 (A) Pre-operative expanded right labium with tissue expander. Urogenital sinus is scarred. **(B)** Post-operative normal appearance of genitalia with conspicuous clitoris and a large Hegar dilator (arrow) in the vagina.

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Continent Urinary Reservoir in Exstrophy/Epispadias Complex

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Summary—The outcome of 15 children and young adults who underwent reconstruction of continent urinary reservoirs (CUR) from January 1987 to 1990 is presented. Ten patients were male and 5 female with an age range of 3 to 20 years. There were 13 patients with bladder exstrophy and 2 with incontinent epispadias. In 8 cases the urinary diversion was performed for an inadequate bladder capacity following successful closure (3), failed attempted closure (3), female epispadias (1) and following successful urethroplasty in 1 case of male epispadias. A tiny fibrotic bladder plate unsuitable for attempted closure was the indication for diversion in 3 patients. Faecal and urinary incontinence following ureterosigmoidostomy (2 patients) and trigonosigmoidostomy (2) was the reason to consider re-diversion in 4 previously diverted patients. In 10 patients an Indiana pouch was performed. The Mitrofanoff procedure was used in 5 cases with caecum (2), sigmoid colon (2) or transverse colon (1) as the urinary reservoir. All patients are continent on clean intermittent catheterisation with stable renal function. Three patients developed large stones within the reservoir and needed open cystolithotomy. This series supports the efficacy of CUR as an alternative procedure to traditional forms of urinary diversion in the management of selected patients with exstrophy/epispadias complex.

Reconstruction of the lower urinary tract for non-compliant bladders in children with exstrophy/epispadias complex should aim to preserve renal function, achieve urinary continence (without external appliance) and secure as normal life activity as possible for the patient. These objectives can be achieved by the creation of a continent urinary reservoir (CUR). Many forms of CUR are now available and they share 3 essentials: a non-obstructing, non-refluxing upper urinary tract draining into a low-pressure capacious reservoir with an adequate continent catheterisable channel (Mitrofanoff, 1980; Kock *et al.*, 1982; Lilien and Camey, 1984; Thuroff *et al.*, 1985; Duckett and Snyder, 1986; Rowland *et al.*, 1987). However, controversy exists regarding the bowel segment to be used, the antireflux procedure and the continence mechanism.

We report 15 patients with exstrophy/epispadias who underwent continent urinary diversion using the Indiana pouch or Mitrofanoff principle. The criteria for patient selection, surgical procedure and results are presented.

Patients and Methods

Between 1987 and 1990, 15 patients with exstrophy/epispadias complex underwent continent urinary diversion at this hospital. The group included 10 males and 5 females with an age range of 3 to 20 years (median 7.6). Thirteen patients had classic bladder exstrophy and 2 had incontinent epispadias. Nine exstrophic patients had undergone initial bladder closure during the first month of life (3 cases), between 1 and 2 years (2) and after the second year (4). In addition, while 4 patients had only 1 closure, 2 had 2 prior closures and 3 had undergone more than 2 closures. Four exstrophic patients underwent urinary diversion initially by ureterosigmoidostomy (2) and trigonosigmoidos-

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tomy (2). Two children with incontinent epispadias underwent diversion following urethroplasty in 1 male patient and primarily in 1 female. Table 1 shows the factors that led to consideration of urinary diversion in this group of patients.

Both the procedure and responsibility for intermittent catheterisation were taught to the patients and their parents.

Table 1 Indications for Urinary Diversion

Indication	*No of patients* *Boys*	*Girls*
Small bladder capacity		
Following successful exstrophy closure	3	—
Following partial bladder dehiscence	1	2
Following successful epispadias repair	1	—
Initially in incontinent epispadias	—	1
Tiny fibrotic bladder plate	2	1
Faecal and urinary incontinence		
Following ureterosigmoidostomy	2	—
Following trigonosigmoidostomy	1	1
Total	10	5

Surgical technique

Ten patients underwent reconstruction of an Indiana pouch (9 with bladder exstrophy and 1 male with epispadias). The first step in the diverted patients was to take the ureterosigmoidostomy or trigonosigmoidostomy with the adjacent area of sigmoid colon resected to reduce the risk of cancer. The ureters were dissected from the bowel with great care to preserve both length and blood supply. The ileocaecal segment was mobilised with the hepatic flexure. A segment of caecum and ascending colon about 15 to 25 cm long (according to the patient's age) with its blood supply based on the ileocolic vessels was detached from the colon. The ileum was divided about 15 cm from the ileocaecal valve. An anastomosis was done between the proximal ileum and transverse colon in 2 layers. The entire length of caecum was then opened along its antimesenteric border. A long submucosal tunnel was created by blunt dissection of the posterior wall of the caecum and each ureter was led in separately. A careful anastomosis of the spatulated end of the ureter to the colonic mucosa was done using interrupted 5/0 chromic sutures. Ureteric drainage was afforded with an 8F paediatric feeding tube in which extra side holes had been cut and the tube was brought through the anterior wall of the reservoir, where it was secured with purse string suture of 3/0 chromic. The caecum was then folded on itself to form the reservoir and was closed in one layer with 3/0 vicryl suture. A large Malecot catheter (22–24F) was left in the reservoir and brought through its anterior wall.

The reservoir was confirmed as water-tight. The terminal ileum was plicated, starting at the ileocaecal valve, with a 10–12F catheter left in the lumen. The plication was carried out using an inner layer of interrupted 3/0 silk Lembert sutures placed 8 to 10 mm apart followed by a second layer of running 3/0 silk to reinforce the first layer. The ileal stoma was placed at the umbilicus (in 3 patients after its excision with a plug of subcutaneous tissue) or at the left lower abdominal quadrant (in 7 patients) and was secured to the skin. Considerable time was spent to ensure easy catheterisation.

The Mitrofanoff principle was used in 5 patients (4 with bladder exstrophy and 1 female with epispadias). The reservoir was fashioned from detubularised caecum (2 patients), detubularised sigmoid colon (2) and detubularised transverse colon (1). Ureteric reimplantation was performed submucosally in the posterior wall of the reservoir. The appendix was isolated with a flange of caecum left on its end to provide a stoma. The caecal opening was closed. The tip of the appendix was amputated and the appendix tunnelled into the taenia and its distal end was anastomosed to the reservoir mucosa with 5/0 chromic sutures. The proximal end of the appendix was brought to the abdominal wall, where it was sutured to the skin. The detubularised bowel was then closed in a U-shaped configuration to create a spherical pouch.

A Malecot catheter was left in the reservoir to facilitate drainage and saline irrigation was performed every 8 h to remove excess mucus. The ureteric stents were removed about 2 weeks postoperatively. At the end of a 3-week period, opacification of the reservoir was done to ensure no leakage. With the tube clamped the patient was allowed to begin self-catheterisation through the stoma. The Malecot catheter was removed several days later when the patient was confident of his ability to catheterise and empty the pouch completely.

The patient was discharged from hospital with instructions to irrigate the reservoir to remove excess mucus twice daily and to perform self-catheterisation every 2 h, progressively increasing the interval between catheterisation during the following months. Urine analysis was done every month and repeat urinary tract radiographic studies were performed at intervals of 1, 3 and 6 months and then yearly.

Results

Early complications included prolonged paralytic ileus in 1 patient which resolved spontaneously after 10 days. Two patients developed a transient leak from the reservoir that needed 2 to 3 weeks to close spontaneously with drainage (Table 2). Excessive mucus production by the pouch was evident in all patients in the immediate post-operative period and was managed by saline irrigations.

Table 2 Complications and Results of Continent Urinary Reservoir

	No. of patients
Early complications	
Prolonged paralytic ileus	1
Urine leak	2
Excess mucus	15
Late complications	
Stricture at ureterocolic reimplantation	1 (1 ureter)
Reflux at ureterocolic reimplantation	1 (2 ureters)
Febrile urinary tract infections	2
Gross haematuria	2
Excess mucus	5
Reservoir calculi	3
Continence on CIC	15
Stable renal function (BUN and serum creatinine)	15

Follow-up of these patients ranged from 9 months to 5 years. Continence as measured by a dry interval of 3 to 4 hours was achieved in all cases. No catheterisation was needed during the night. Reservoir distension was accompanied by vague abdominal fullness or cramping which signalled the necessity for emptying. No difficulty in performing intermittent catheterisation was reported either by the patients or their parents. The average reservoir capacity ranged from 150 to 600 ml. Gradual dilatation and an increase in the volume of the bowel pouch was noted in all patients (Fig. 1). Renal function as measured by BUN (blood urea nitrogen) and serum creatinine has remained stable in all patients. Radiographic examinations revealed stable upper urinary tracts in 13 patients (Fig. 2), improvement in 1 patient (with pre-operative hydroureteronephrosis) and deterioration in 1 patient. This last patient (20 years old) developed a stricture at the anastomosis of the left ureter and reservoir with recurrent episodes of pyelonephritis. He underwent endoscopic dilatation of the stricture successfully. A 5-year-old male with a Mitrofanoff procedure developed bilateral grade II reflux that disappeared on chemoprophylactic agents within 2 years. Many of our patients have bacteriuria, yet febrile urosepsis occurred in only 2. Transient gross haematuria without infection occurred in 2 patients (1 needed blood transfusion) and resolved sponta-

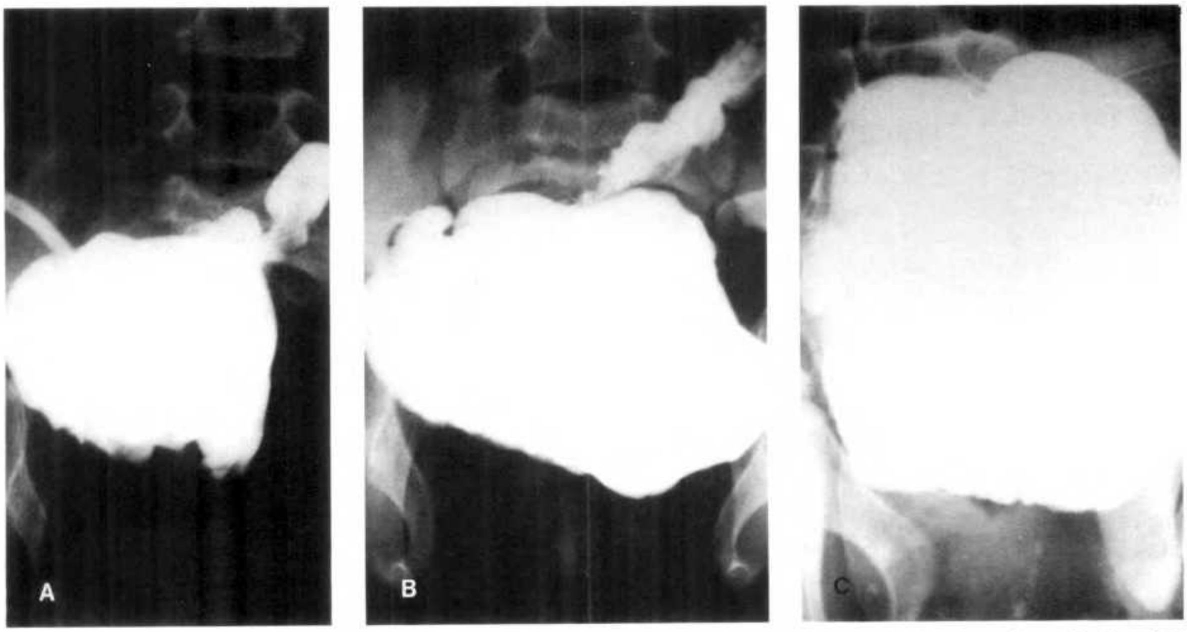

Fig. 1 Opacification of an Indiana pouch in a 9-year-old exstrophic patient. Progressive increase in the reservoir capcity from 150 to 500 ml within 2 years. Consequently the time interval between catheterisation increased from 3 to 6 h.

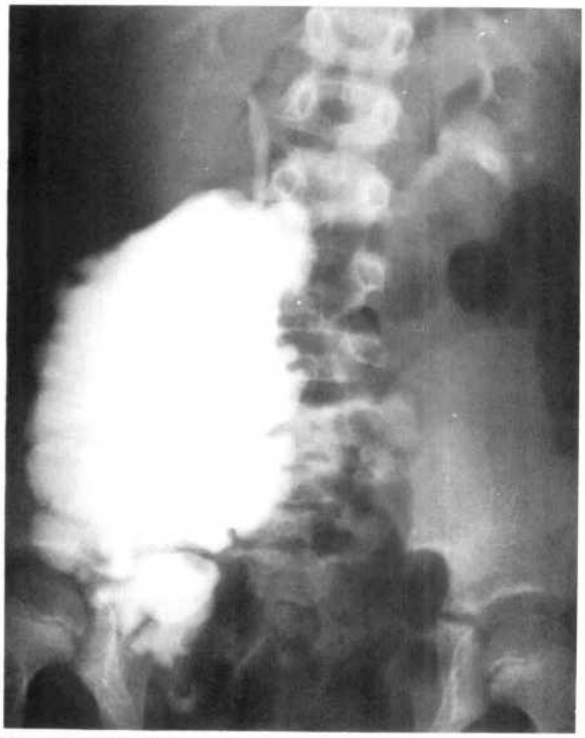

Fig. 2 IVU of 3-year-old female exstrophic patient who underwent continent diversion using detubularised transverse colon with appendix as a catheterisable channel (Mitrofanoff). A normal upper urinary tract drains into a capacious reservoir.

neously. No electrolyte imbalance has been observed to date.

Excessive mucus production by the reservoir after 6 months was present in 5 patients. Three of them developed large stones within the pouch (2 to 4 years post-operatively) which required open removal. Table 2 summarises the complications and functional results of urinary diversion.

Discussion

The creation of a continent urinary reservoir to replace absent components of the lower urinary tract in patients with exstrophy/epispadias complex has improved the quality of life for these unfortunate children. To resemble the function of the normal lower urinary tract, reconstruction should provide a capacious low pressure reservoir, protection to the upper urinary tract and secure a dependable continent catheterisable channel. A variety of methods exists to achieve these goals. Almost all segments of the bowel can be used and each has its enthusiasts and opponents. Detubularisation of the bowel segment and closing it in a U-shaped configuration to produce a spherical pouch will inhibit the generation of pressure waves produced by peristalsis or mass contraction of the isolated segment, producing a low pressure capacious reservoir that gradually dilates and provides maximum capacity for the length of the bowel used (Goldwasser and Webster, 1986; Koff, 1988). Protection of the upper urinary tract can be achieved by a careful antireflux attachment of the ureters to the reservoir by the technique of Leadbetter (1951) or Goodwin *et al.* (1953). Reconstruction of a dependable continent catheterisable channel is an integral part of CUR. A plicated, tailored or intussuscepted small bowel segment, appendix and ureter (Mitrofanoff), detrusor tubes (Kroop and Angwafo, 1986) or skin tubes can be used. In addition, the recognition and acceptance of clean intermittent catheterisation by patients as an effective method of producing low pressure emptying of the bowel reservoir through the catheterisable channel drew attention to CUR (Lapides *et al.*, 1972).

In the present series we used the Indiana pouch and Mitrofanoff principle to achieve continent urinary diversion. Ten patients had Indiana continent reservoirs (a reconfigured caecum). The continent channel was achieved using plicated terminal ileum without nippling. The Mitrofanoff principle (use of the isolated reversed vascularised appendix) as a catheterisable channel was used for 5 patients whose reservoirs were fashioned from detubularised caecum, transverse colon or sigmoid colon. A transcolonic submucosal tunnelling of the ureters into the reservoir was carried out in all 15 patients (Goodwin *et al.*, 1953). This technique was successful in the protection of the upper urinary tract in all 30 ureters reimplanted except in one ureter which needed dilatation, and 2 ureters showed temporary reflux.

The advantages of the Indiana and Mitrofanoff procedures are obvious. Reconstruction and dependability of the catheterisable continent channel mechanism are achieved more easily than with other methods of urinary diversion. They have the advantage of separating the urinary tract from the faecal stream.

Mucus production has remained a problem for 5 of our patients for more than 6 months despite daily saline irrigations. Three of them developed large stones that required open removal. Although metabolic disorders due to increased contact time of urine with the absorptive bowel mucosa have not been encountered until now, this remains a potential threat (Mohler, 1988). Bacteriuria has been a frequent finding, yet febrile urinary tract infection was present in only 2 patients.

Our initial results with both the Indiana CUR and the Mitrofanoff procedure are encouraging with regard to continence and preservation of renal function. Close long-term follow-up of these patients is essential, since the late sequelae of such operations are not known with certainty at the present time.

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Electron Microscopic Observations on the Exstrophic Bladder Wall Muscle

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The bladder wall muscle of children with bladder exstrophy was investigated by electron microscopy in order to reveal the microhistological structure of the smooth musculature. Biopsy specimens were taken during reconstructive surgery, cut into 2 × 1 × 1 mm blocks and immersed in fixative immediately after cessation of blood supply. Fixation was achieved with 2% phosphate buffered glutaraldehyde (method A) or 5% colloidin buffered glutaraldehyde (method B). Osmium tetroxide was used for post-fixation and the blocks were rehydrated in graded ethanol. Samples were embedded in epoxy and cut into ultrathin sections which were mounted on copper grids, stained with uranil acetate and lead citrate and examined by a JEOL 100-B or JEOL 100-C electron microscope. Normal microhistological patterns of bladder musculature were revealed (Fig.): smooth muscle cells were filled with dark stained thick myosin and light stained actin myofilaments and scattered cell organelles. Close contacts joined muscle cells and pinocytotic activity indicated sites of close contacts that were not observed on the level of section. Collagen and elastic fibres were seen in the intercellular matrix. Nerves were apparent amid muscle bundles. Dark stained (catecholamine-containing) and "empty-like" (acetylcholine-containing) granules were observed in nerves.

It was concluded that the microhistological architecture of exstrophic bladder musculature is able to contract and relax. No sample was obtained on follow-up, so that late observations on the bladder smooth muscle layer are not available and it is difficult to conclude whether or not it is impaired.

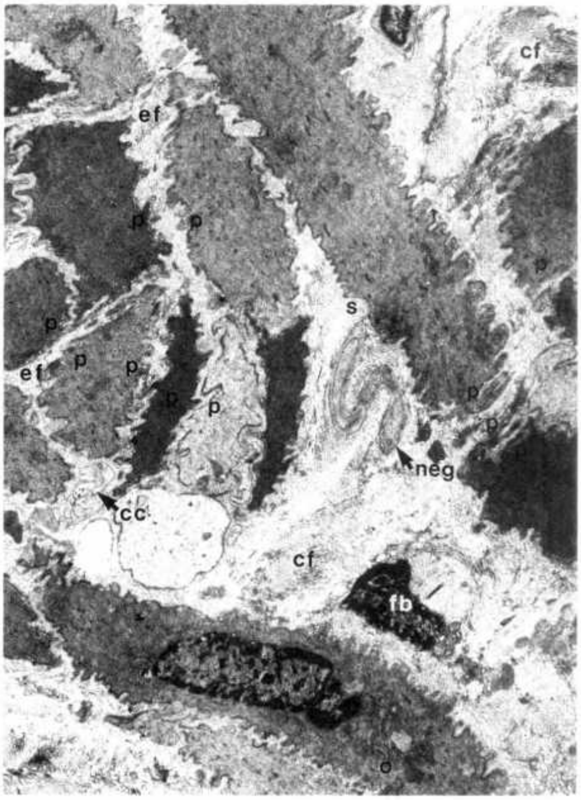

Fig. Electron micrograph of exstrophic bladder smooth muscle layer. Muscle cells are filled with dark stained thick myosin and light stained thin actin myofilaments and scattered cell organelles (o). Close contacts (cc) join muscle cells at the end of muscle bundles. Pinocytotic activity (p) is remarkable. Schwann cell coated nerve with "empty-like" granule (neg) lies between muscle cells and a fibroblast (fb) is also observed. Elastic fibres (ef) and collagen fibres (cf) dominate the intercellular matrix. (Method A: uranil acetate and lead citrate × 2000).

Prune-belly Syndrome: An Almost Extinct Disease

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The classic triad of manifestations in prune-belly syndrome (absence of the anterior abdominal muscles, bilateral intra-abdominal testes and anomalies of the urogenital tract) and associated anomalies are frequently classified in 3 grades. Grade I represents the full blown picture in association with respiratory, gastrointestinal, orthopaedic and neurological problems or other major malformations which make survival unlikely. Grade II represents the characteristic triad alone and grade III the external features, intra-abdominal testes and almost

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normal urinary tract. In 1978 Woodward published his first report on the survival of all grade II cases of prune-belly syndrome treated with extensive urogenital surgery and normally placed testes with transabdominal orchiopexy in all grade II and III cases.

We present our experience with 6 cases in the last 12 years, with a follow-up of 4 to 12 years.

Five patients had the complete syndrome: 1 had severe bilateral renal dysplasia and was born with renal failure (grade I) and the other 4 had normal or borderline renal function (grade II). One patient had the external features and intra-abdominal testes, but a normal urinary tract (grade III).

Cardiac, pulmonary and orthopaedic problems were excluded in all patients. Initial evaluation included blood urea and creatinine levels, renal and bladder ultrasonography, intravenous urography and/or DTPA renography. Neither cystography nor retrograde catheterisation was performed prior to surgery.

Primary urogenital reconstructive surgery was carried out in all 5 patients with urological abnormalities; this included excision of the distal two-thirds of both ureters, remodelling of the remaining upper third, ablation of the bladder dome, bilateral transabdominal orchiopexy and bilateral ureteric reimplantation. The grade III patient underwent bilateral transabdominal orchiopexy only.

The grade I patient died during the second year of life despite early urological reconstruction (at the age of 4 days) and chronic peritoneal dialysis for end-stage renal failure; all other patients are presently under surveillance.

One of the grade II patients required further reduction pyeloplasty for progressive dilatation of the pelvicaliceal system and another underwent unilateral nephrectomy of a dysplastic non-functioning kidney. Eight of 9 ureters show neither obstruction nor reflux, 1 patient has grade II unilateral vesicoureteric reflux with normal ipsilateral kidney function, and 10 of 10 testes are in a normal scrotal position and growing. All surviving children have normal renal function (as shown by laboratory and isotopic evaluation), adequate physical and psychological development and lead normal social lives.

Despite the poor outcome of grade I patients as reported in the literature, we believe that long-term results with grade II and III patients (who form the great majority) are quite good and that early extensive genitourinary reconstruction is the best treatment for these grades of prune-belly syndrome.

Two-stage Reconstruction of Bladder Exstrophy

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We perform functional reconstruction of bladder exstrophy as follows. First stage—primary closure with reconstruction of the abdominal wall (with osteotomy except in neonates). Second stage—bladder neck reconstruction with urethroplasty and reconstruction of the external genitalia at age 3 to 4 years.

Between 1981 and 1991, 102 children with bladder exstrophy were treated in this Centre; in 20 cases surgery at other hospitals had been unsuccessful and urinary diversion was carried out here.

Primary bladder closure, regardless of bladder size, was performed in 82 patients (mean age 3.4 months). There were 20 new-born babies, 12 of whom were operated on without osteotomy during the first 24 hours of life. Bladder dehiscence as a complication of primary reconstruction was observed in 7 children. All underwent surgery successfully 1 year later.

The second stage of functional reconstruction (Young-Dees-Leadbetter method) was performed in 43 children (mean age 4 years 4 months). Vascularised preputial island flap urethroplasty with elongation of the corpora cavernosa was carried out in 29 boys and vulvoplasty in 14 girls; 27 of these patients were dry for at least 2 to 3 hours.

During the second stage of the procedure, bladder augmentation (colocystoplasty) was performed in 8 patients because of small bladder capacity. The outcome was that 2 girls and 1 boy remained dry for 3 hours on intermittent self-catheterisation, 2 boys were partially continent and voided by abdominal pressure, and 3 boys had indwelling catheters. We feel that this modification is not satisfactory in boys because of difficulty in catheterisation. In boys with a small bladder we now undertake urethroplasty with elongation of the corpora cavernosa at the second stage. Follow-up suggests that bladder capacity is increasing and we hope to be able to perform bladder neck reconstruction without augmentation in the future.

It was concluded that 2-stage reconstruction of bladder exstrophy is a good method of treatment, especially in children with adequate bladder capacity. In boys with small bladder capacity the 3-stage procedure seems to be more beneficial than the 2-stage procedure with colocystoplasty

Scintigraphic Study of Pelviureteric Junction Obstruction in Children: What is Wrong with the Diuretic Test

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The diuretic test is widely used for the differential diagnosis between atonic and obstructive dilatation of the upper urinary tract. It has recently been criticised because of the high rate of false-positive results for obstruction; it is believed that the test is reliable only when it excludes and not when it confirms obstruction.

Since starting to use this test we thought that changes in renal urine content caused by micturition could contain important information. The duration of the scintigraphic test could therefore be shortened and the diuretic test avoided if all of the procedures (orthostatism, micturition, diuresis renography) were organised as a diagnostic protocol.

If renography revealed an obstructive pattern, patients were included in the following protocol:

(1) Orthostatism for 5 min followed by 1-min scan.
(2) Micturition followed by 1-min scan.
(3) Diuresis renography (15-min dynamic scan).
(4) Same as (1) and (2).

Data were expressed as a percentage of variation of renal activity; a decrease $\geqslant 20\%$ was taken to indicate adequate urinary tract patency.

The results showed that the diuretic test could be avoided in almost half of the patients. Patients with better renal function (glomerular filtration rate) responded earlier (first step of the protocol). They are therefore expected to respond better to the tests and in these cases the diagnostic protocol can be shortened. Orthostatism (*i.e.* gravitational effect) is the most important factor (more important than micturition) in promoting urinary flow through a dilated urinary system.

Varicocele at Puberty: Its Effect on Testicular Volume

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The correlation of varicocele and infertility is a well known phenomenon. The earliest appearance of varicocele is at puberty. The varicocele causes the testes to become smaller as the child grows, making the boy a possible candidate for an infertile man.

To estimate the incidence of varicocele and to show its effect on the testes, we screened 340 boys aged between 10 and 14 years for varicocele and also measured testicular volume. The incidence of varicocele was 11.5%, which is lower than for the adolescent and adult population. At age 14 years this rate was nearly the same as for the adolescent varicocele groups. Most varicoceles were grade I (44%), only 18% were grade III. The average volumes for left and right testes were 10.154 ± 0.664 and 10.215 ± 0.778 ml respectively. There was no statistically significant difference between these volumes and also between the varicocele and non-varicocele groups ($P > 0.001$). Only in grade III varicocele was the difference between the testes significant ($P < 0.001$).

Varicocele at puberty has a low incidence and low grade in most cases. The disease does not seem to affect both testes. In order to decide upon prompt treatment one must check the volume of both testes as well as the grade and duration of the disease.

The Genital Aspects of Exstrophy

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The importance of achieving continence in patients with bladder exstrophy and epispadias has resulted, in our experience, in attention being concentrated on the urinary tract, with the genital tract usually receiving secondary consideration. We have studied this aspect in 81 patients during the last 20 years. Among our 23 females we felt there was more concern about their cosmetic and genital defects than their wetness. Three problems worried them: hypogastric defects, cleft vulvas and abnormal vaginas. We performed 13 full-thickness abdominoplasties and 4 omphaloplasties. The mons veneris, vulva and hemiclitoris were corrected in 13 patients and 5 patients with pediculated or hypertrophic labia underwent reductive surgery. Fourteen females went through puberty: 8 had vaginoplasty; pregnancy followed without problems in 2 married patients.

Among our 58 males, 48 underwent genital reconstruction at the second-stage procedure; 10 are still waiting for treatment to be completed. Unsightly short penis and doubts about satisfactory function were responsible for their "sexual anxiety". Three criteria were used to classify reconstruction: position, lengthening and erection. The position was evaluated as good if the penis was straight or downward. Forty patients were included in this category (after 1 or 2 procedures) and 8 require further procedures.

The lengthening of the penis was evaluated in 17 patients who volunteered to measure their penis before and after reconstruction; this ranged from 10 to 40 mm (mean 18). Normal erectile function was preserved in 47 patients, 28 have a satisfactory straight erection and 19 have a significant dorsal or lateral deformity that requires a further procedure.

This review has emphasised the importance of considering these aspects Meticulous attention to the technical aspects of reconstructive surgery at an early age can usually result in normal genital function and a good cosmetic appearance in most patients.

Testosterone-secreting Capacity of the Testis in Pre-pubertal Boys with Undescended Testis

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In a previous study we observed children with undescended testis (UT) to determine the frequency of testicular hypoplasia/dysplasia and fusional disorders between the testis and epididymis which might cause later infertility. Of 1195 investigations the above anomalies were found in 40.4%. The ability to secrete testosterone (T) was examined in a selected group of patients with these anomalies. The aim of the study was to determine whether any of the following factors were associated with impaired T secretion in UT: (1) testicular hypoplasia; (2) fusional anomaly between the testis and epididymis; (3) intra-abdominal location of the testis; (4) hypospadias.

Thirty boys age 2 to 11 years (mean 6) were examined. The examination was carried out only in the case of bilateral testicular hypoplasia (suspected at investigation or confirmed at operation) in bilateral non-palpable testes and in hypospadias associated with UT. Ten children had bilateral abdominal cryptorchidism, 7 had bilateral inguinal cryptorchidism and 3 had bilateral anorchia. Ten boys had hypospadias of varying degree, with bilateral UT in 7 and unilateral UT in 3. All children received 1500 IU chorionic gonadotrophin administered over 3 consecutive days; serum T values were measured before and 24 hours after the third injection and were established with radioimmunoassay.

Only 7 of 27 children with UT had T responses <2.0 nmol/l (stimulated T levels below this value were regarded as low; their values ranged between 0.5 and 1.21 nmol/l (mean 0.77)). In 3 patients both the T levels and the size of their testes became normal at puberty. The mean T value of the entire group was 4.16 nmol/l (range 0.5–14.5 nmol/l); this is within the normal range, but according to others it is below the level measured in healthy boys. There was no marked difference in stimulated T values of children with (4.18 nmol/l) or without (4.15 nmol/l) hypospadias. The mean T level in intra-abdominal testes was higher (5.43 nmol/l) than in inguinal testes (2.36 nmol/l). This may be due to the fact that while in inguinal testes the testicular hypoplasia is established before the operation, the non-palpable intra-abdominal testes are often of normal size and consistency. The difference was marked with regard to testicular size: in patients with bilateral testicular hypoplasia the mean T value was almost one-third (2.33 nmol/l) of those with normal testes (6.82 nmol/l). In bilateral fusional anomalies the mean T level (2.35 nmol/l) was also significantly lower than in patients with intact fusion between the testis and epididymis (4.37 nmol/l).

It was concluded that in cryptorchidism the ability of the Leydig cells to produce testosterone is within normal limits in most cases and on many occasions even in patients with testicular hypoplasia. Moreover, the size of a hypoplastic testis and its ability to produce testosterone can become normal at puberty. Pre-pubertal castration for hypoplastic testis is therefore contraindicated in cryptorchidism.

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Case Reports

Spontaneous Thrombosis of the Left Spermatic Vein

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Case Report

A 45-year-old man presented with a 2-week history of left groin pain and swelling. He was otherwise asymptomatic and had a previous history of left-sided epididymitis. On examination he was apyrexial and had an extremely tender left spermatic cord mass at the level of the superficial inguinal ring. The left testis and epididymis were normal to palpation and there was no evidence of an inguinal hernia. Urine analysis and intravenous urography were normal. A diagnosis of left funiculitis was made and the patient was treated with Tarivid (ofloxacin) 300 mg *b.d.* The patient's pain rapidly resolved but he had a small, hard residual left inguinal mass after 1 month. An inguinal exploration was performed which revealed a thrombosed varicocele in an otherwise normal left spermatic cord. The thrombosed vessels were excised and the patient made an uneventful recovery. Histological examination (Fig.) showed a thrombus in a large vein with evidence of organisation.

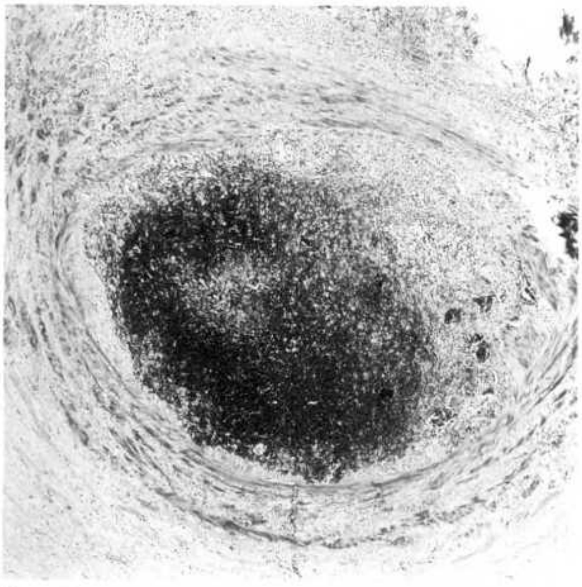

Fig. Venous thrombosis with organisation. (H and E × 4).

Comment

The differential diagnosis of a groin mass includes varicocele, hydrocele, spermatocele, hernia, spermatic cord haematoma, primary and metastatic tumour and thromboangiitis obliterans (Isenberg *et al.*, 1990). To date only 5 cases of spontaneous spermatic vein thrombosis have been reported (McGavin, 1935; Anseline, 1977; Vincent and Bokinsky, 1981; Isenberg *et al.*, 1990). The patients ranged in age from 19 to 57 years and in each case the left side was involved. In one case vigorous exercise preceded the thrombosis. The precise aetiology of the condition is unknown and having a palpable varicocele does not seem to play a role as none of the patients had had varicoceles. Although it has been suggested that bed rest, heat and possibly anticoagulation may be adequate therapy, it is preferable that surgical exploration with excision of the thrombosed vessels be performed, especially if a residual mass remains following initial conservative therapy (Vincent and Bokinsky, 1981). The consideration of this entity in the differential diagnosis of a spermatic cord mass should prevent the surgeon performing an orchiectomy, as was done in 2 of the previously reported cases (McGavin, 1935).

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Ureterocolic Fistula due to Transitional Cell Carcinoma of the Ureter

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Case Report

A 59-year-old man presented with a history of dysuria and pneumaturia associated with night sweats, weight loss and general malaise. In addition he gave a history of pain in the right loin which radiated down the anterior aspect of his right thigh. On examination, there was some tenderness in the right loin but no other abnormality was found.

Urine culture showed a coliform urinary tract infection and he had a raised white cell count of 28×10^9 cells/l. A plain abdominal X-ray was unremarkable.

Abdominal ultrasound showed a mass in the right iliac fossa, associated with right ureteric dilatation (Fig. 1). The right kidney was hydronephrotic and contained a rather poorly defined solid mass at the upper pole. Computed axial tomography of the abdomen and pelvis confirmed the presence of both the renal mass and the mass in the right iliac fossa, but it also showed that the latter seemed to communicate with the sigmoid colon. A gas fluid level was seen in the bladder (Fig. 2). Aspiration cytology of the right renal mass showed malignant transitional cells with squamous metaplasia.

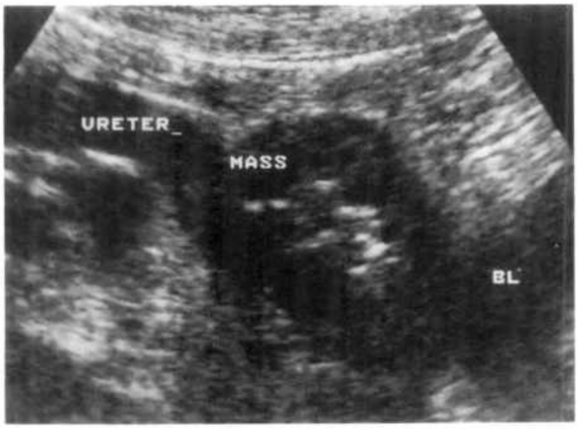

Fig. 1 Ultrasound scan demonstrating the right ureter communicating with the right iliac fossa mass, which in turn communicates with the bladder (BL).

At laparotomy a large pelvic abscess communicating with and obstructing the right ureter was found. This mass also communicated with the sigmoid colon, which was macroscopically otherwise normal. The right renal mass was confirmed, and a right nephroureterectomy was carried out, together with a Hartmann's procedure. Pathological examination showed the presence of a moderately differentiated transitional cell carcinoma arising from the right renal pelvis. There was a second similar tumour in the lower ureter which had eroded into the sigmoid colon and had resulted in a ureterocolic fistula. Although the renal tumour was completely resected, histology suggested that resection of the ureteric tumour was incomplete.

The patient made a good recovery initially, but after 7 weeks his condition deteriorated, he became septicaemic and died. Autopsy showed residual tumour in the right iliac fossa, encasing the iliac vessels.

Comment

Prior to 1930, the commonest cause of ureterocolic fistula was tuberculosis (Abeshouse, 1949), but in recent years the most common aetiological factor has been ureteric calculi, although rarer causes include diverticulitis, war trauma and surgical trauma (Mogg, 1962; Heney and Crooks, 1984). Symptoms include pneumaturia and the intermittent passage of faecal particles. The urine is

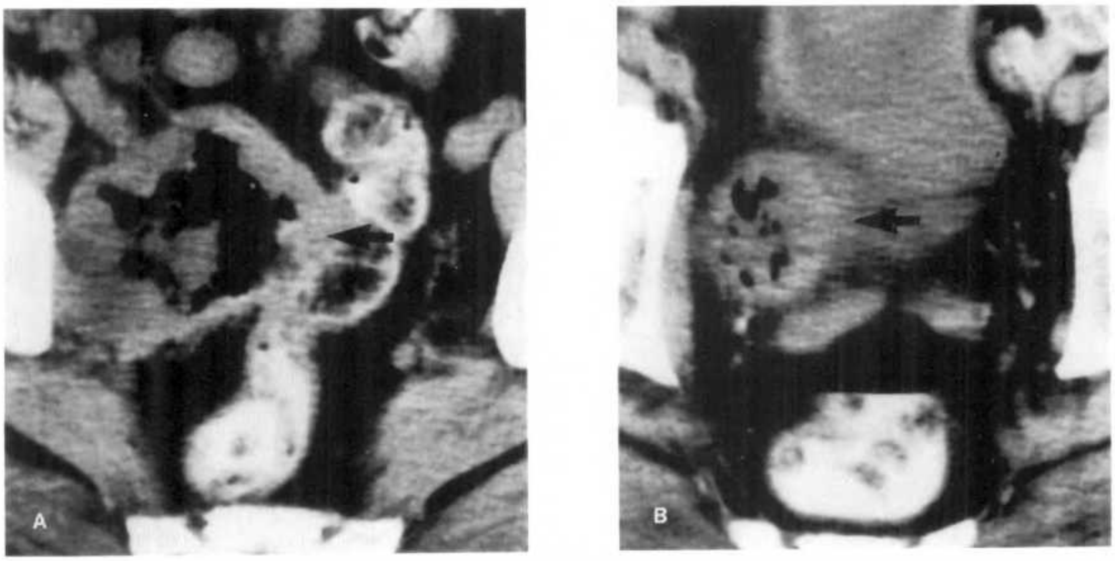

Fig. 2 Pelvic CT scans. (A) The right iliac fossa mass can be seen to communicate with the sigmoid colon (arrow). (B) At a different level, the mass communicates with the bladder (arrow) and an air fluid level within the bladder can be seen.

constantly infected and symptoms of cystitis or pyelonephritis may be present. Diagnosis, which is often difficult, may be made from the history, usually in conjunction with intravenous urography, which may show hydronephrosis and in a proportion of patients may visualise the fistula. The use of barium enema or retrograde pyelography may be helpful in outlining the pathological process.

We believe this to be the first reported case of transitional cell carcinoma of the ureter causing a ureterocolic fistula; it demonstrates both the difficulties in diagnosis and the poor outcome of invasive ureteric tumours.

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Human Penile Ossification

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Human penile ossification is rare and few cases have been described in the literature. Earlier reports lacked histological evidence (Frank *et al.*, 1989). Two cases of penile ossification are described; the first was due to blunt penile trauma and was associated with impotence and the second occurred after partial amputation of the penis for carcinoma.

Case Reports

Case 1. A 42-year-old male presented with a 3-month history of pain and a hard plaque on the shaft of the penis near the base. He also complained of erectile impotence. Three months earlier he had sustained blunt trauma during intercourse, following which he developed the plaque and erectile impotence.

On examination the mass at the base of the penis measured 3.4 × 2.2 cm. It was irregular, partially mobile and involved the corporal tissue with subcutaneous extension. There was no chordee and the scrotum and testes were normal. X-ray confirmed the zone of ossification in the base (Fig. 1). Dynamic cavernosometry demonstrated a venous leak in the dorsal vein (Fig. 2). Exploration revealed a hard, bony plaque involving both corpora, under the tunica albuginia; it was excised completely. The dorsal vein was ligated and excised for 3 cm. Histopathological examination confirmed the ossification. The patient made a good recovery and reported improvement in erection.

Case 2. A 46-year-old male presented with a 6-month history of difficult micturition and interrupted stream. He had undergone partial amputation of the penis for carcinoma 3 years previously. Examination revealed a hard fixed mass at the meatus of the amputated penis extending to the base and measuring 4 × 2.5 cm. No inguinal lymphadenopathy was found. Recurrence was suspected and total amputation with perineal urethrostomy was carried out. Histopathology revealed an ossified mass and no malignancy.

Comment

Many animals have normal bone formation in the glans penis which helps copulation (Bett, 1952). Human penile ossification is unusual and less than 15 histologically proven cases have been reported (Wespes *et al.*, 1985; Frank *et al.*, 1989). Conditions associated with os penis include trauma (Joffe, 1961), Peyronie's disease (Gulati *et al.*, 1974),

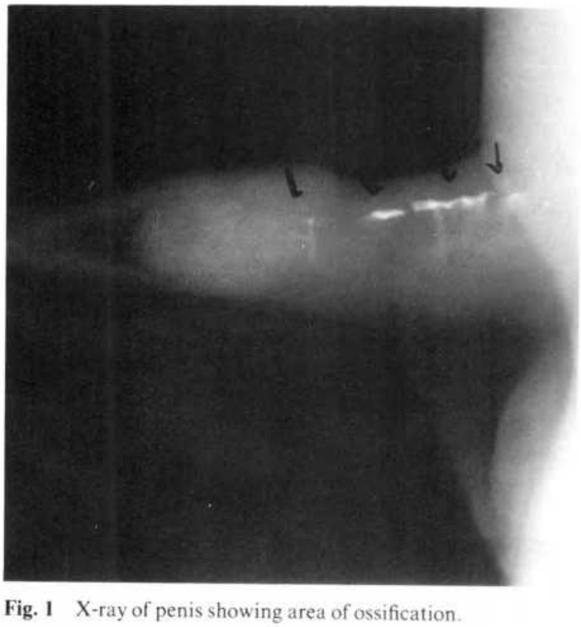

Fig. 1 X-ray of penis showing area of ossification.

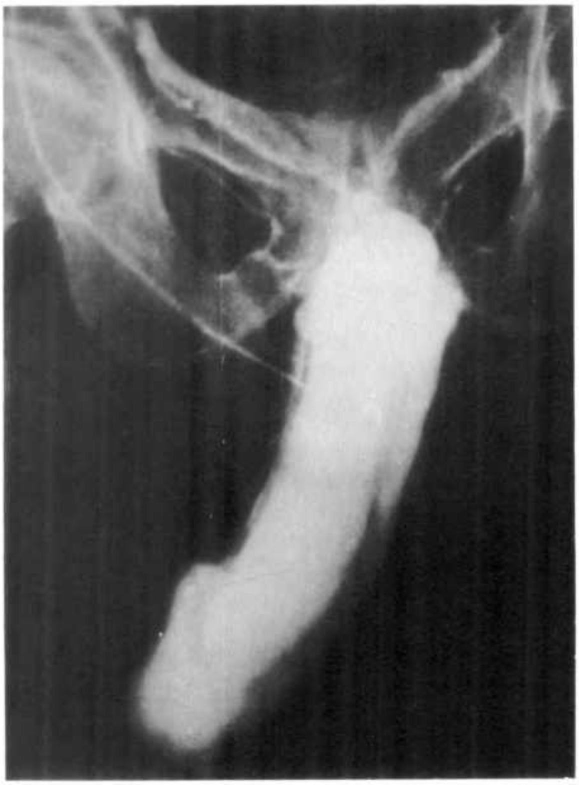

Fig. 2 Cavernosography showing venous leak in dorsal vein-internal iliac vein (major leak).

malignancy (Morgan, 1966) and a congenital origin (Champion and Wegrzyn, 1964).

The present report is the first to describe 2 cases of true penile ossification. The first patient had a history of blunt trauma and his impotence was due to a venous leak which probably resulted from the trauma. In the second case there was no relevant aetiology other than a history of penile carcinoma. It is not known what triggered the bone formation. We suggest that fibrosis occurs initially and continuous stimulation of this leads to proliferation and metaplasia. Osteoid tissue may then be formed.

It is a benign condition and excisional biopsy is adequate, but if removal is not complete the remaining bone may resume the process of ossification.

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Intravesical BCG Therapy: A Potential Hazard for Medical Staff

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Intravesical BCG (Bacillus Calmette-Guérin) therapy for bladder cancer was introduced by Morales *et al.* (1976) and has proved to be effective in the treatment of carcinoma *in situ* and recurrent superficial tumours of the bladder (Lamm, 1988). It seems to be superior to other chemotherapeutic agents such as thiotepa, doxorubicin and mitomycin C. It is cost effective (Heron and Rønne, 1989).

We present a case report that emphasises the potential hazards of BCG for the medical personnel who handle it.

Case Report

A 54-year-old healthy nurse pricked herself on the back of the left index finger with a needle previously used to prepare a BCG solution. Twenty-four hours later she experienced pain and 4 days later a suppurative lesion developed. Further examination revealed tender, enlarged lymph nodes in the ipsilateral axilla.

The abscess was excised. Histological examination revealed epithelial granuloma containing Langhans cells (Fig.); inoculation of the pus revealed acid-fast mycobacterium. The diagnosis of tuberculous suppuration due to BCG was confirmed and treatment with isoniazid and rifampicin was instituted.

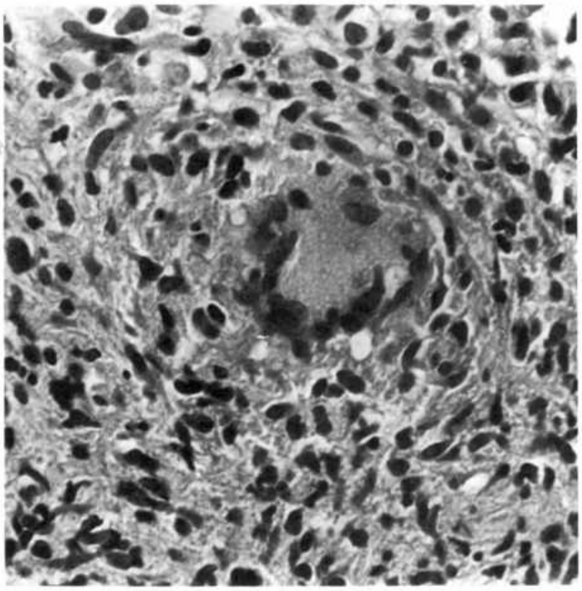

Fig. Biopsy from the abscess revealing epithelial granuloma and Langhans cell. (H and E × 250).

X-rays of the left hand and lungs were normal. The lesion on the left hand healed uneventfully, though antibiotic treatment was withdrawn after 10 days because of adverse neurological reactions.

Clinical and X-ray examination of the lungs 12 months later revealed no evidence of local or disseminated disease.

Comment

BCG consists of freeze-dried, live attenuated bovine tubercle bacilli and the strain used in this case was Danish 1331. BCG is used clinically as a vaccine against tuberculosis and is administered by intradermal injection in a dose of 0.1 ml. Superficial ulceration at the injection site is a well known complication and sometimes concomitant enlarged regional lymph nodes are seen. Tubercular abscess formation is rare, although osteomyelitis and generalised infection have been reported. Vaccination with BCG is therefore contraindicated in patients with immune deficiencies (Orihuela *et al.*, 1987). In this department BCG therapy for carcinoma *in situ* and widespread recurrent superficial cancer of the bladder is instituted 2 weeks after transurethral resection of all bladder tumours and is instilled intravesically weekly for 6 weeks as a solution of 120 mg BCG in 50 ml saline.

We wish to stress that BCG solutions must be prepared with great care and all medical staff must be aware of the hazards.

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Unusual Nodule Arising from the Vas Deferens

J. M. ORRELL, *Department of Pathology, Ninewells Hospital and Medical School,* and J. P. A. WEAVER, *Department of Urology, Royal Infirmary, Dundee*

Case Report

A 52-year-old man presented with a painful nodule in the left groin. There was no previous history of vasectomy, other surgery or trauma in that area. On exploration a glistening nodule 15 × 10 × 10 mm was seen apparently arising from the vas deferens. A 40-mm length of vas was excised to include this nodule. In longitudinal section the lesion was multiloculated and contained gelatinous material (Fig. 1). The gelatinous material expanded the lumen of the vas to each side of the nodule. Histologically the lesion was divided by fibrous septa. Over most of their surface the fibrous septa were devoid of epithelium but in places there were small strips of cuboidal epithelium (Fig. 2). Special stains confirmed the contents to be mucin. The epithelium of the adjacent vas also appeared attenuated. Within the fibrous septa there was minimal chronic inflammation and no sperm were identified.

Comment

There are very few primary pathological conditions of the vas deferens. These include sperm granulomas and vasitis nodosa (Young and Scully, 1986).

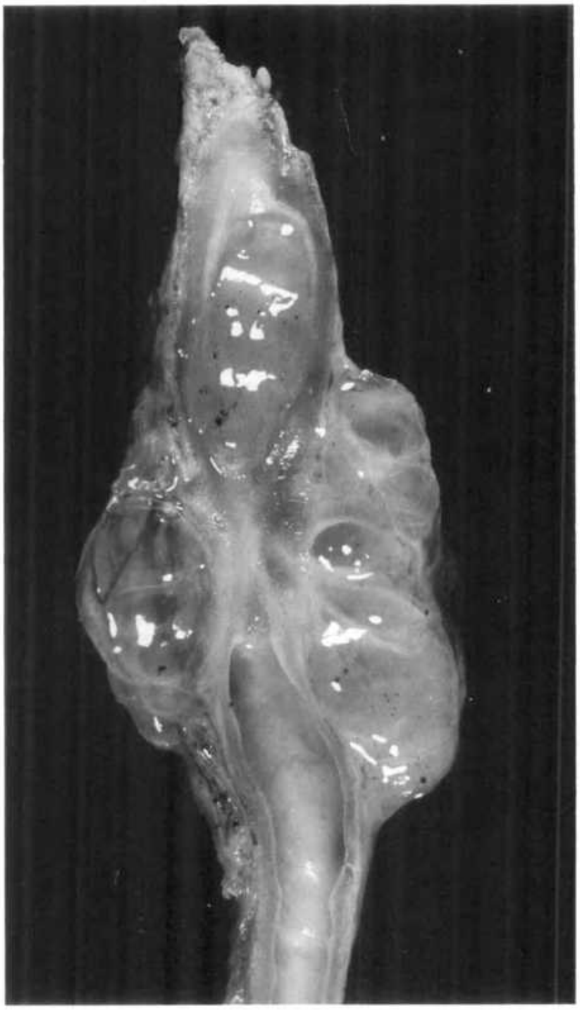

Fig. 1 Gelatinous nodule arising from the vas deferens (× 4).

Previous vasectomy or trauma are often found to be aetiological factors. In this case there was neither the clinical history nor the histological features of these 2 conditions. Our interpretation of the findings is that the nodule arose as a consequence of chronic obstruction of the vas deferens with accumulation of secretions proximal to the obstruction forming the multiloculated nodule. We have not found a previous description of such a lesion in the literature.

Acknowledgement

We acknowledge the opinion of Dr K. Grigor, Department of Pathology, University of Edinburgh.

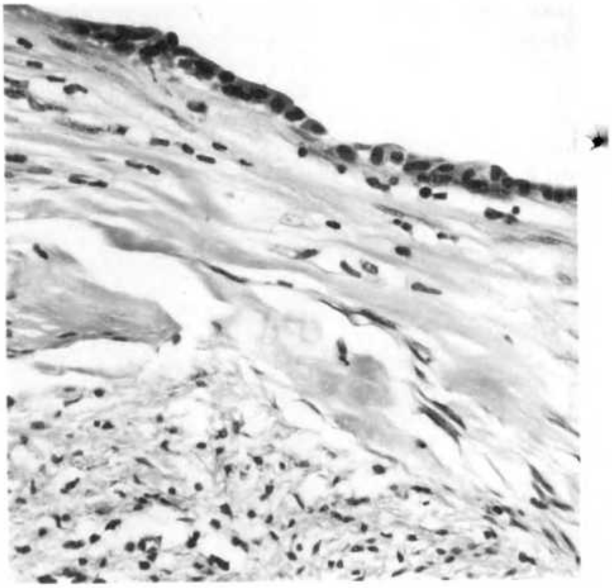

Fig. 2 Fibrous septa lined by cuboidal epithelium (H and E × 300).

Reference

Young, R. H. and Scully, R. E. (1986). Miscellaneous neoplasms and non-neoplastic lesions. In *Pathology of the Testis and its Adnexa*, ed. Talerman, A. and Roth, L. M. Pp. 121–122. London, Edinburgh: Churchill Livingstone.

Requests for reprints to: J. M. Orrell, Department of Pathology, Ninewells Hospital and Medical School, Dundee DD1 9SY.

Primary Small Cell Carcinoma of the Augmented Urinary Bladder

J. GOLOMB, K. J. LEWIN, J. B. deKERNION and S. RAZ,
Department of Surgery, Division of Urology, and
Department of Pathology, Division of Surgical Pathology,
UCLA School of Medicine, Los Angeles, USA

Case Report

A 20-year-old female with urinary incontinence secondary to hypospadias underwent failed reconstructive surgery followed by cutaneous urinary diversion, and 9 years later staged undiversion with ileocystoplasty was performed. She did well on self-catheterisation for 7 years, when severe irritative voiding symptoms and frequent urinary tract infections occurred. Cystoscopy revealed a necrotic tumour covering the bladder base and the anastomotic site. There was no clinical evidence of a paraneoplastic syndrome. Biopsy was consistent with a high grade invasive carcinoma and radical cystectomy with urinary diversion was accomplished. The specimen contained an ulcerating bladder tumour, about 5 cm in diameter, invading through the muscularis into the perivesical fat, without involvement of the attached bowel segment and the regional lymph nodes. Histologically there were solid sheets and nests of mitotically active small cells (Fig. 1) with focally positive argyrophil silver stain (Grimelius) (Fig. 2) and chromogranin immunohistochemical stain compatible with the diagnosis of small cell carcinoma.

Comment

Primary small cell carcinoma is one of the rare non-transitional cell carcinomas of the urinary bladder reported to date in 17 patients and partly reviewed by Swanson *et al.* (1988). In none of the reported cases had augmentation cystoplasty been performed. Small cell carcinoma is assumed to arise from cells that closely resemble the argentaffin (Kulchitsky's) cells found in the alimentary tract. These cells contain neurosecretory granules characteristic of gastrointestinal endocrine cells and are distributed widely throughout the body, including the genitourinary organs. The occurrence of primary small cell carcinoma of the urinary bladder following augmentation may be coincidental, although it has been suggested that augmentation cystoplasty may play a predisposing role in tumour formation, mainly adenocarcinoma, via recurrent urinary tract infections which result in enhanced production of highly carcinogenic nitrosamines by gram-negative bacteria (Filmer and Spencer, 1990). It is noteworthy that in our case the attached bowel segment was not involved by tumour, ruling out a carcinoid tumour of the alimentary tract as the primary malignancy.

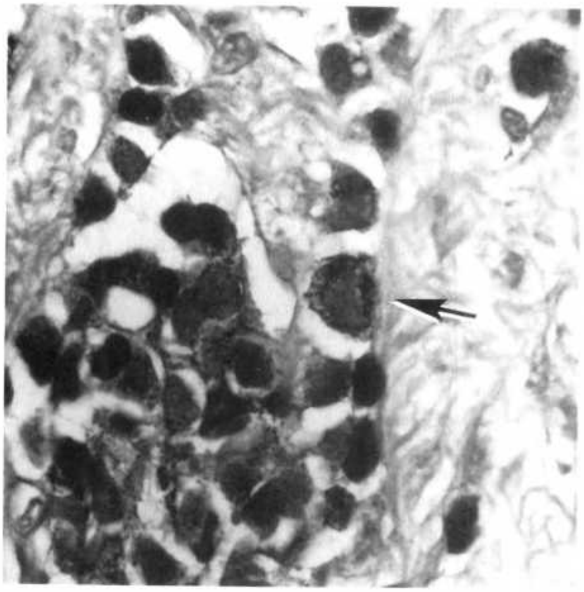

Fig. 2 Grimelius (silver) stain, demonstrating the fine argyrophilic staining of the tumour cells (arrow). (Silver stain × 500).

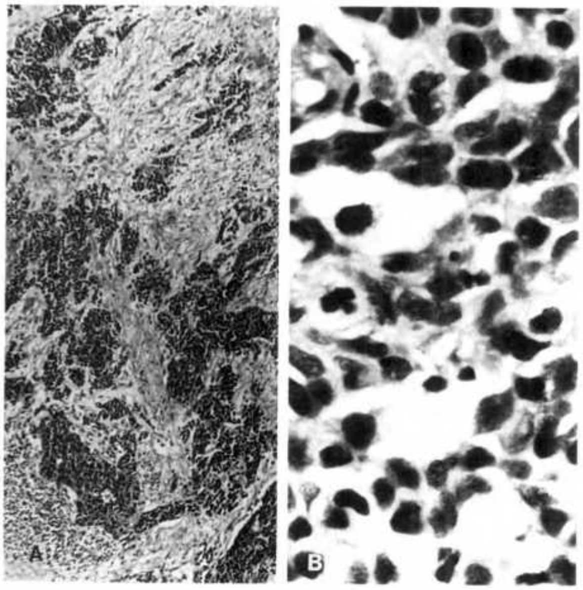

Fig. 1 Small cell carcinoma of the bladder. (A) Low power magnification shows irregular nests of darkly staining cells, diffusely infiltrating the fibrovascular stroma (H and E × 60). (B) Higher magnification of the tumour is characterised by irregular, hyperchromatic, finely stippled nuclei and scant cytoplasm (H and E × 300).

References

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Swanson, P. E., Brooks, R., Pearse, H. *et al.* (1988). Small cell carcinoma of urinary bladder. *Urology*, **32**, 558–563.

Requests for reprints to: J. Golomb, Department of Urology, Edith Wolfson Medical Center, Holon 58100, Israel.

Verruciform Xanthoma of the Penis

R. N. LONSDALE, *Department of Histopathology, Norfolk and Norwich Hospital, Norwich*

Case Reports

Case 1. A 44-year-old man presented with a 1-year history of a slowly growing lesion on the ventral surface of the shaft of the penis. A pale brown warty papule (0.8 cm in diameter) thought to be a viral wart was excised.

Case 2. A 66-year-old man with chronic eczema and ichthyosis had a 2-year history of a preputial growth (Fig. 1). Examination disclosed an extensive verrucous lesion of the undersurface of the prepuce which was incompletely excised at circumcision.

In both cases histological examination revealed verrucous hyperplasia of the epidermis enclosing dermal papillae containing numerous "foamy" lipid-filled macrophages (Fig. 2). The epidermis was infiltrated by neutrophils with superficial micro-abscesses. Dense chronic inflammation with lymphoid follicles was present in the dermis. There was no epidermal atypia.

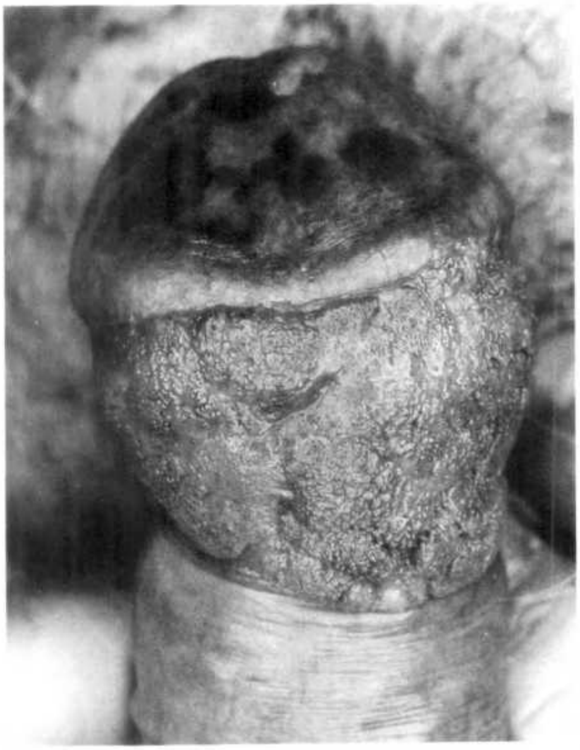

Fig. 1 Preputial growth.

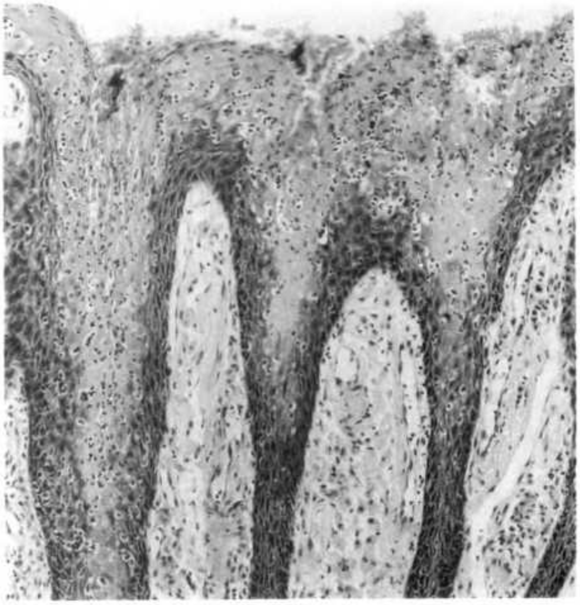

Fig. 2 H and E × 100.

Comment

Verruciform xanthoma (VX) usually occurs in the oral cavity of adults. Extra-oral lesions are very rare, with only 2 reported cases arising on the penis (Kraemer *et al.*, 1981; Ronan *et al.*, 1984). The aetiology is unknown: hypotheses include local irritation and viral infection (Neville, 1986). VX has arisen in epidermal naevi and chronic dermatoses (as in case 2) and is probably an unusual reaction to a variety of epidermal abnormalities. Only one case has been reported in hyperlipidaemia. The lesion appears benign and excision is curative.

Clinically, VX may be confused with a viral wart, squamous carcinoma, verrucous carcinoma or seborrhoeic keratosis. The histopathological features are usually diagnostic. However, a small biopsy containing scanty foam cells may be misdiagnosed as a verrucous carcinoma.

Acknowledgements

The author thanks Mr C. G. C. Gaches and Dr C. Grattan, Norfolk and Norwich Hospital, for permission to report these patients.

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Neville, B. (1986). The verruciform xanthoma. A review and report of eight new cases. *Am. J. Dermatopathol.*, **8**, 247–253.

Ronan, S. G., Bolano, J. and Manaligod, J. R. (1984). Verruciform xanthoma of penis. Light and electron-microscopic study. *Urology*, **23**, 600–603.

Requests for reprints to: R. N. Lonsdale, Department of Histopathology and Morbid Anatomy, Level 5, Clinical Laboratories, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

Sclerosing Lipogranuloma of the External Male Genitalia

J. GOLOMB, J. KOPOLOVIC and Y. SIEGEL, *Departments of Urology and Pathology, Edith Wolfson Medical Centre, Holon, Israel*

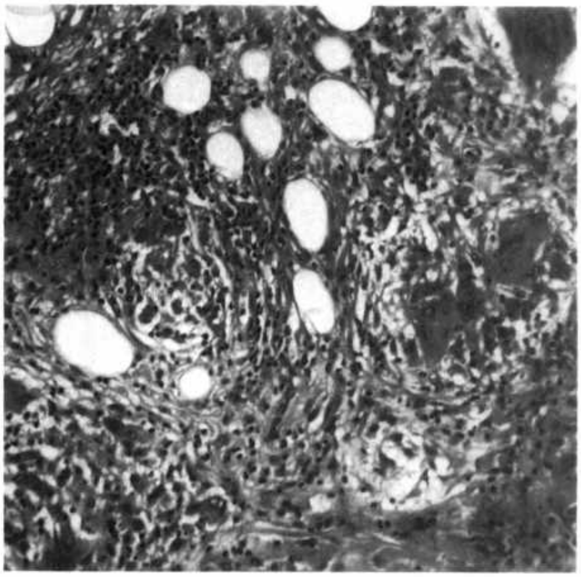

Fig. Epithelioid granuloma with giant cells containing lipid vacuoles and lymphocytic infiltration. (H and E × 100).

Case Report

A 37-year-old Caucasian male presented with a painless scrotal mass. He denied voiding symptoms, genital trauma or any local use of dermatological preparations. On examination a non-tender scrotal mass was palpated, located in the midline caudal to the penoscrotal junction; it was of rubbery consistency, was not attached to skin or scrotal contents and measured 3 × 4 × 3 cm. Urine analysis and blood chemistry were normal. The mass was explored and found to be loosely adherent to the surrounding structures; it was resected completely. On macroscopic examination it was grayish and had a greasy and nodular appearance. Microscopically, it consisted of fatty tissue with granulomatous inflammation. In some areas extensive necrosis was present. The granulomas consisted of multinucleated giant cells containing lipid vacuoles. Fibrosis and lymphohistiocytic infiltration with many eosinophils were also seen. Stains for acid-fast bacilli and fungi were negative. The histological features were consistent with sclerosing lipogranuloma (Fig.). The post-operative course was uneventful and at follow-up 3 months later there was no evidence of local recurrence.

Comment

Sclerosing lipogranuloma of the male external genitalia has been reported following the injection of foreign bodies such as paraffin, mineral oil or silicone, or the external use of vitamin E or "baby oil". Earlier reports concluded that sclerosing lipogranuloma was an inflammatory response to endogenous lipid degeneration. Matsuda *et al.* (1988) reported 4 patients with clinical features similar to those of our patient. They analysed the granulomas and found no evidence of exogenous lipids. However, in a case of paraffin lipogranuloma Nakamura *et al.* (1985) reported markedly different results following chemical analysis of the granuloma tissue using similar techniques.

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Nakamura, M., Sakurai, T., Yoshida, K. *et al.* (1985). Sclerosing lipogranuloma of the penis: chemical analysis of lipid from the lesional tissue. *J. Urol.*, **133**, 1046–1048.

Requests for reprints to: J. Golomb, Department of Urology, Chaim Sheba Medical Centre, Tel-Hashomer 52621, Israel.

British Journal of Urology (1992), **70**, 576–577

Point of Technique

The "Nipple" Urethral Orifice Following Total Penectomy

T. C. GOEL and D. DALELA, *Department of Surgery, King George's Medical College, Lucknow, India*

After undergoing total penectomy the patient voids from the perineal urethrostomy, which has the disadvantages of the need to squat, soiling of clothes and skin, urinary dermatitis (Goel, 1986) and dysuria due to meatal stenosis (Sawhney, 1967). We describe the reconstruction of a urethral orifice like a nipple to circumvent these problems.

During total penectomy a 3–4 cm urethral stump is conserved. A hole is made in the perineal skin by raising a lateral skin flap (Fig. 1A). The urethra is brought out (Fig. 1B) and the extramucosal spongy tissue trimmed from its distal half. To achieve this, a 20 F urethral catheter is inserted and stay sutures applied to the tip of the urethra to stabilise and stretch it (Fig. 1C). The latter helps to minimise bleeding during subsequent steps. In the middle of the urethral stump a partial thickness circumferential incision is made in the corpus spongiosum. Two longitudinal incisions are then made through the same thickness at 12 o'clock and 6 o'clock in the distal half and the 2 resultant flaps are sharply dissected off, care being taken to avoid mucosal damage (Figs 1D–E). A slit is made on the side of the lateral skin flap and the debulked urethra is everted on to the proximal half (Fig. 1F). The oozing from the raw urethral surface stops immediately. Fine catgut sutures or minimal diathermy are occasionally required. The sheath of the inner urethra is anchored to the subcutaneous tissue to prevent its retraction. These sutures are placed only in the anterior half of the circumference with only

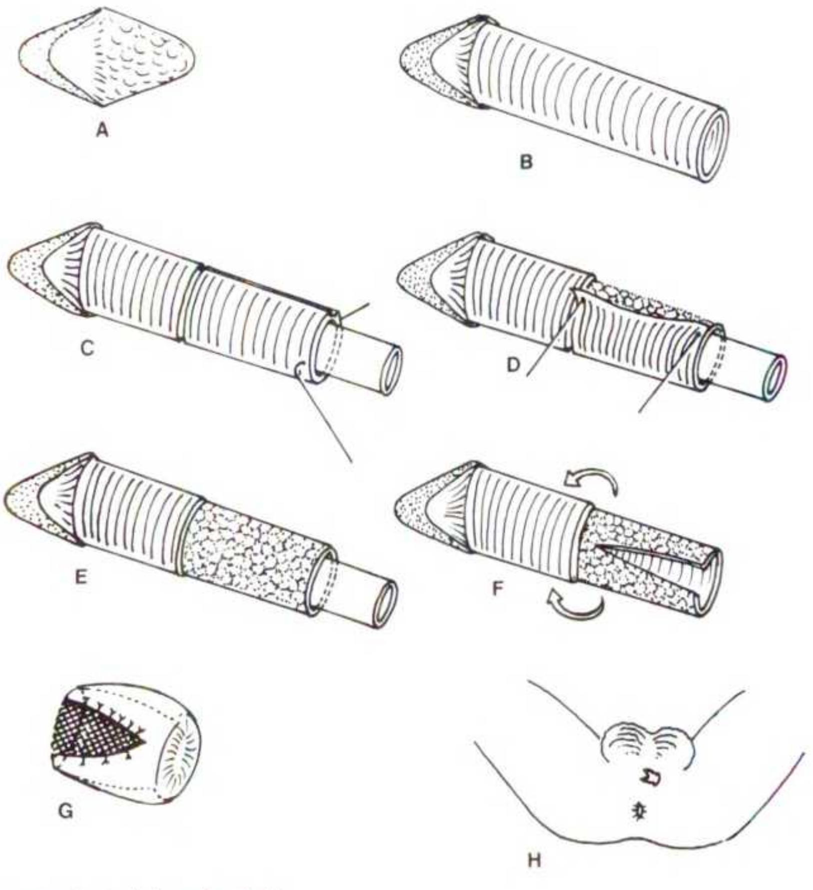

Fig. 1 Details of the operative technique (see text).

1 suture at 6 o'clock to allow drainage from the posterior side. The urethral edge is stitched to the edge of the buttonhole by finely placed 4/0 chromic catgut sutures. The lateral skin flap is fed into the gap of the uncovered urethra resulting from slitting and eversion. The sutures on the posterior limb of the flap are fewer in number and left slightly loose to allow extrusion of any collection. No drain or urethral catheter is left in place. Thus a 1.5 cm urethral nipple is formed, one lateral sector of which is formed by the skin flap. If the scrotum is retained, it is advanced pre-pubically. The area is dressed with antibiotic and vaseline gauze.

Comment

This technique is simple, though some practice may be required for urethral debulking. The lateral skin flap breaks the circumferential suture line. Postoperatively, the patient is able to urinate with a good stream in the standing posture (Fig. 2). The scrotum is kept away either manually or by prepubic advancement. There is no meatal stenosis and no extra care is required other than application of an emollient.

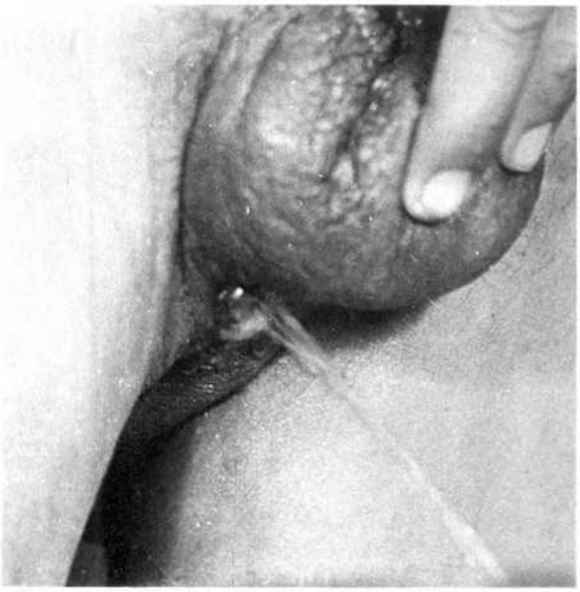

Fig. 2 Upright micturition from the "nipple" urethral orifice.

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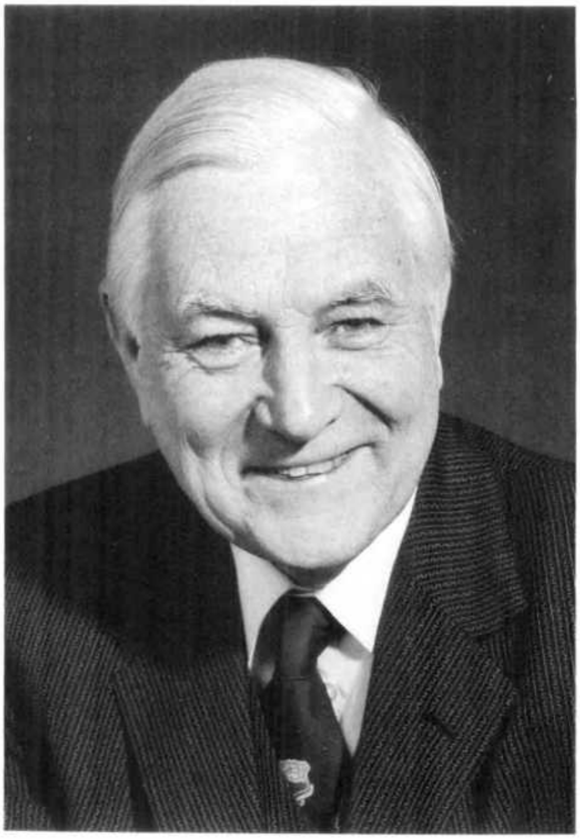
British Journal of Urology (1992), **70**, 578–579

Obituary

Mr W. Keith Yeates, MD, MS, FRCS, FRCSEd



Keith Yeates, who died on 26 July 1992, was Editor of this Journal from 1973 to 1978, Chairman of the Editorial Committee from 1978 to 1984, and Consulting Editor from 1985 to 1990. He was also President of the British Association of Urological Surgeons from 1980 to 1982. No-one should underestimate the impact of this quiet, polite, erudite Scots-born Northumbrian on British urology: his influence will long be remembered and appreciated.

Almost the whole of his professional career was based in Newcastle. His medical school was King's College Newcastle, University of Durham, and post-graduate training was at Newcastle General Hospital and one year at St Peter's Hospital, London.

Keith Yeates was appointed consultant to the Royal Victoria Infirmary in Newcastle at the relatively young age of 31 and he gave 34 loyal and productive years to Newcastle and his specialty. He soon built a formidable reputation in urology and andrology and the thoughtfulness behind his work was well recognised by his appointment as Editor of the British Journal of Urology in 1973. Keith Yeates brought to the Journal a large number of changes that were typical of the person: tightening of the style, attention to detail, more explicit instructions to authors (which he knew well were never read by most would-be authors) and always the emphasis on the need for the highest standards. Some will not know that Keith Yeates' own standards were set by his personal motto "Everything can be improved". The British Journal of Urology in the 1970s under Keith Yeates became a highly professional publication which he continued to aid and nurture as Chairman of the Editorial Board.

Keith Yeates had no wish to be a quantity contributor in urology but always the emphasis was on quality. He had that disarming style of asking questions about almost anything (from surgical techniques to questions for interviews) but they were always questions which most persons thought they understood but usually did not. The outcome of this approach was no better exemplified than by one of the best analyses of that ill understood problem of scrotal pain (*Br. J. Hosp. Med.*, **33**, 101–104, 1985). He was also aware that there was a high level of misunderstanding concerning bladder dysfunction and andrology and in his writing he succeeded in making these subjects more intelligible and relevant. He gave much thought to subjects such as rules and regulations but only to get it right and to avoid confusion. In 1983 he was awarded the St Peter's Medal by the British Association of Urological Surgeons and he earned this easily on his own criterion for the award, which was "without whom British urology would not be what it is today".

Visiting Professorships, guest lectureships and principal lectureships in all parts of the globe became part and parcel of his later career: he enjoyed these offers and honours and gave his full enthusiasm to each occasion, so that his contributions were always marked by original and personal input. He also gave the same thought and originality to after dinner speeches.

In the 1980s, post-graduate training in the United Kingdom underwent many changes. As Chairman of the Speciality Advisory Committee and then as the first Chairman of the Intercollegiate Board in Urology (1984–1988), Keith Yeates held a most important role in the development of a specialty examination in urology. Indeed it was because he was able to steer his colleagues through some difficult times that the concept of intercollegiate examinations was finally established. He funded the Keith Yeates Medal to be given to the best candidate taking the FRCS (Urology). In 1985 the Royal College of Surgeons of Edinburgh awarded Keith Yeates an FRCSEd without examination—a recognition which he greatly enjoyed.

If urology appeared to absorb all of Keith Yeates' life this impression was wrong: his tastes in music were catholic, he was a serious collector of contemporary Scottish painting and he was an expert in Newcastle silver and he enjoyed his close knit family; but above all he revelled and excelled in activities of the mind.

The ultimate test came when he knew of his own demise: medical texts abound with rarities and Keith Yeates died of one of those affecting the lungs. He knew of the inevitable several years ago but told almost no-one. He had strong personal views, based on careful thought, on life and death. This Journal benefited from his positive guidance and readers will want to acknowledge both his scholarship and humanity. We who follow wish to ensure that his modesty never obscures his contributions; his precision of thought will remain an ideal for future generations.

G.D.C.

British Journal of Urology (1992), 70, 580

Notices

British Association of Urological Surgeons
President: J. C. Smith, MS, FRCS

Annual Meeting: Harrogate, 22–25 June 1993

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1992. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 8th January 1993.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

Urological Research Society

The first meeting of the Urological Research Society (formerly the Guy's Annual Research Meeting) will take place at Guy's Hospital, London, on Friday, 8 January 1993. Further information about attendance and the presentation of papers from Professor A. R. Mundy, Academic Department of Urology, Guy's Hospital, St Thomas' Street, London SE1 9RT. Tel: 071-955 4659. Fax: 071-955 4675.

Institute of Urology and Nephrology (University College London) in association with St Peter's Hospital

Preliminary Academic Programme 1992/1993

4 November 1992
Platelets and Endothelium in Renal Disease

11 December 1992
Urolithorama

11–22 January 1993
Short Courses in Urology and Nephrology (including Urological Cancers; Upper Tract Obstruction; Stone Disease; Prostatic Disease; Trauma)

11 February 1993
Uro-radiology

February 1993
Advances in Minimally Invasive Surgery

15–18 March 1993
Uro-andrology

19–20 March 1993
International Symposium of Operative Andrology

March 1993
New Techniques in Prostatic Outflow Obstruction

April 1993
Urology for the FRCS

19 April–7 May 1993
Short Courses in Urology and Nephrology (including Female Urology; Reconstructive Surgery; Paediatric Urology; The Elderly; Tropical Diseases; Urology of the Future)

For further information please contact: The Course Secretary, Institute of Urology and Nephrology, 48 Riding House Street, London W1P 7PN. Tel: 071 380 9381/9372.

British Journal of Urology (1992), **70**, 581–582

Diary

1992

November 1–4	Third International Workshop on Carcinoma *in situ* and Cancer of the Testis. Copenhagen, Denmark. Contact: Workshop Secretariat, c/o Professor N. E. Skakkebaek, University Department of Growth and Reproduction, Section 5064, Rigshospitalet, 9 Blegdamsvej, DK-2100, Copenhagen, Denmark.
November 8–10	Fourth International Conference of the Society for Minimally Invasive Therapy. Dublin, Ireland. Contact: Professor J. Fitzpatrick, 47 Eccles Street, Dublin 2, Ireland. Tel: +353-1-308530. Fax: +353-1-300345.
November 27–28	International Postgraduate Course on Reconstructive Surgery of the Lower Urinary Tract in Children. Amsterdam, The Netherlands. Contact: Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands: Tel: +31 20-566 4801. Fax: +31 20-696 3228.
December 4–5	Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.

1993

January 26–29	Ninth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev, Denmark. Contact: Dr F. Rasmussen, Department of Urology, Herlev Hospital, DK-2730 Herlev, Denmark.
March 14–15	State-of-the-Art Genitourinary Ultrasound Course. Honolulu, Hawaii. Contact: American Institute of Ultrasound in Medicine, Convention Department, 11200 Rockville Pike, Suite 205, Rockville, Maryland 20852, USA. Tel: (301) 881-2486. Fax: (301) 881-7303
March 19–20	Second European Congress on Ambulatory Surgery. Brussels, Belgium. Contact: Dr C. De Lathouwer, Brussels One Day Clinic, Avenue du Duc Jean 71–73, B-1080 Brussels, Belgium. Tel: +322/424.1212. Fax: +322/425.7076.
March 27	First International Symposium on Bladder Cancer. "BCG immunotherapy in superficial bladder cancer. The 1993 state of the art". Padova, Italy. Contact: Professor F. Pagano, Department of Urology, University of Padova, Via Guistiniani 2, 35128 Padova, Italy. Tel: 049-8212720. Fax: 049:8212721.
April 19–22	2nd Interamerican Meeting on Pediatric Urology. Viña Del Mar, Chile. Contract: Dr Ricardo Gonzalez, 420 Delaware Street, S.E. Box 45, University of Minnesota Hospital, Minneapolis, Minnesota 55455, USA. Tel: 612 625-9117. Fax: 612 626-2458 *or* Dr Ricardo Zubieta, Esmeralda 678, 3 er Piso, Of. 303, Casilla 639, Santiago, Chile. Tel: 56-2-331. Fax: 56-2-391 085.
May 16–20	American Urological Association, San Antonio Convention Centre, San Antonio, Texas.

June 4–5	Fifth International Meeting of Andrology. "Corporal Veno-occlusive Dysfunction: Diagnosis and Treatment". Rome, Italy. Contact: Dr Diego Pozza, Centro di Andrologia e di Chirurgia Andrologica, via Flaminia Nuova 280, 00191 Rome, Italy. Tel. and Fax: +39.6-3270741.
June 20–24	Canadian Urological Association Annual Meeting, Bonaventure Hotel, Montreal, Quebec. Contact: To be announced.
September 26–30	International Symposium on Sex Hormones and Anti-hormones in Endocrine-dependent Pathology: Basic and Clinical Aspects. Milan, Italy. Contact: M. Motta or M. Serio, Department of Endocrinology, University of Milan, 9 Via Balzaretti, 20133 Milan, Italy. Tel. 02-20406576. Fax: 02-29404927.
November 4–6	Second International Congress of the Dutch Urological Association. "New Insights into the Aetiology, Diagnosis and Management of BPH". Amsterdam, The Netherlands. Contact: IMEDEX, P.O. Box 3283, 5203 DG 's-Hertogenbosch, The Netherlands. Tel: +3173429285. Fax: +3173414766.
1994	
May 15–19	American Urological Association, Moscone Centre, San Francisco, California.

British Journal of Urology (1992), **70**, 583

Book Reviews

Advances in Urology. Volume 4. Edited by B. Lytton, W. J. Catalona, L. I. Lipshultz and E. J. McGuire. Pp. xiv+220. St Louis, Baltimore, Boston, Chicago, London, Philadelphia, Sydney, Toronto: Mosby Year Book. 1991. Price: £47.00

Volume 4 in this Series, published in 1991, sustains the excellent standards set by its predecessors. This volume contain 12 reviews covering new technology (cavitron resection of the prostate, balloon dilatation of the prostate, genitourinary laparoscopy), medication for stones, for the male reproductive system and for prostate cancer, and various topics including immunotherapy using BCG, invasive bladder cancer, renal hypertension, ambiguous genitalia and the pathophysiology of incontinence in the elderly. Each of these subjects is covered by a comprehensive and up-to-date review. This volume gives admirable coverage of contemporary issues in urology and is highly recommended.

Bladder Biopsy Interpretation. (Biopsy Interpretation Series). By L. E. Nochomovitz (with contributions by M. J. Manyak and L. B. Kahn). Pp. xii+225. New York: Raven Press. 1992. Price: US$99.00.

This is a succinct, up-to-date account of bladder pathology and is the latest in the valuable "Biopsy Interpretation Series". The previous book in this series dealing with uropathology was concerned with the prostate (J. I. Epstein) and was of a very high standard. The standard is maintained in the present volume, which covers non-neoplastic and neoplastic conditions. The work is profusely illustrated and the photomicrographs are of good quality. As is to be expected, the bulk of the book is concerned with epithelial neoplasms, the rare variants being well described and illustrated. The author circumvents the vexed question of classifying low grade papillary transitional cell tumours by calling them all Grade 1 carcinomas, thus avoiding the use of the term "papilloma".

There is a useful chapter on the diagnosis and differential diagnosis of spindle cell lesions (L. B. Kahn), lesions which can provide great diagnostic difficulties.

This is a well written and illustrated text which provides an up-to-date summary of the surgical pathology of the bladder. Pathologists dealing with urological specimens will find it a most useful bench book. Urologists also should find it a readable and instructive account of the subject.

Clinical Neuro-urology. Second edition. Edited by R. J. Krane and M. B. Siroky. Pp. xiii+692. Boston, Toronto, London: Little, Brown and Company. 1991. Price: £65.00.

This is not just another theory textbook but a bulging handbook of practical working knowledge. As a compilation of chapters by many acknowledged experts, the book avoids repetition except where this adds to debate and follows a well structured and comprehensive theme.

The section on basic sciences includes excellent new chapters on detrusor muscle and fluid mechanics. There follows a thorough practical discussion of investigative techniques. Coverage of urodynamics is excellent, though ambulatory monitoring and ultrasonographic screening are hardly mentioned. One is also left in some doubt as to whether neurophysiological investigations belong truly in the research laboratory or in the clinical office.

Sections follow on the clinical manifestations of both neurogenic and non-neurogenic vesicourethral dysfunction, including several new chapters. Both non-surgical and surgical treatment are covered, though this last section comprises only 12% of the whole book.

Comprehensive and practical, well illustrated and reasonably priced, this book is undoubtedly a good read and a good buy. However, there are disappointments. A few chapters seem somewhat "compact" set amongst their more lavish companions. One or two of these bear uncomfortably close resemblance to chapters in other books. In general there is a shortage of references from the last 5 years, no doubt a result of publishing delays. This does mean, however, that anyone hoping to use this work as an up-to-date reference source is likely to be disappointed.

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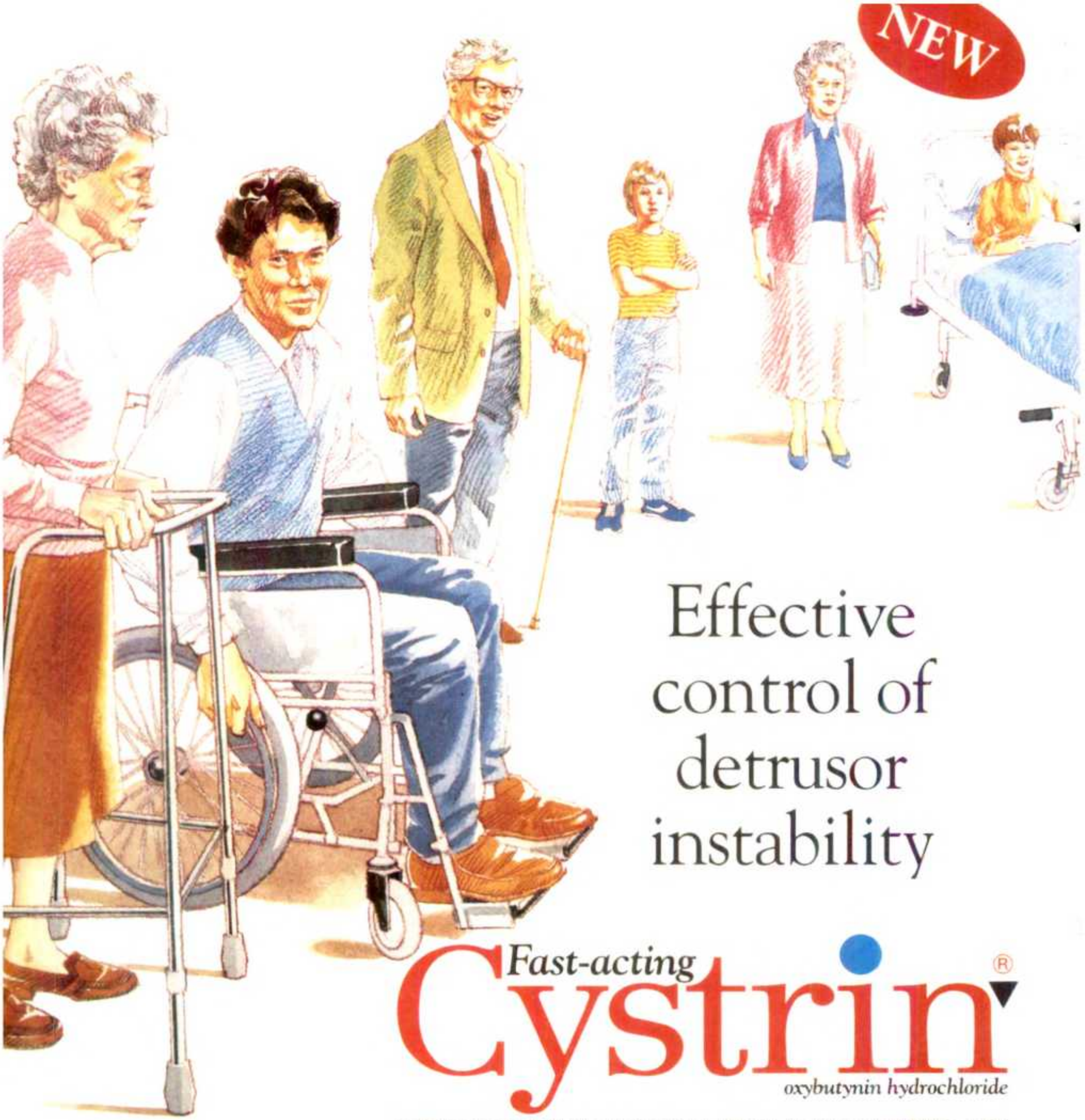

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REVIEW

Tumour Suppressor Genes in Urinary Tract Oncology

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Tumour suppressor genes are a heterogeneous group of genes present in the DNA of normal cells; the proteins encoded by such genes promote cell adhesion and suppress cell transformation and metastasis. The role of deleted or mutated suppressor genes in common adult cancers has been appreciated following studies of certain rare childhood tumours, most notable being the retinoblastoma and nephroblastoma. The multistage model for tumourigenesis requires consecutive genetic (oncogene and tumour suppressor) abnormalities during tumour progression. Such models are emerging for the common urinary tract cancers—kidney, bladder and prostate. The potential role of tumour suppressor genes as prognostic indicators or screening tools in the management of these cancers is discussed.

Cancer may be sporadic or hereditary; indeed, in the case of some cancers previously considered to be sporadic, such as carcinoma of the prostate, there is a significant familial association (Steinberg *et al.*, 1990). Some have become accepted as "model" hereditary cancers, mostly occurring in childhood and best known of which are the retinoblastoma and Wilms' nephroblastoma; studying these rare tumours has led us a considerable way towards understanding the molecular principles of tumourigenesis in a multitude of commoner cancers.

Tumour formation results from loss of the balance between cell division and withdrawal from the cell cycle by differentiation or cell death; tumour invasion and metastasis, hallmarks of malignancy, result from disorders in the interactions between the cells and their surroundings. Signals regulating cell proliferation and interactions come from proteins, such as growth factors and cell adhesion molecules, which are encoded by messenger RNA that is in turn transcribed from genomic DNA. A protein which functions abnormally because of a structural abnormality, or its over- or under-expression, is thus a manifestation of an abnormality of the nuclear DNA. This abnormality may be the presence of an activated oncogene, either acquired by spontaneous mutation or viral infection, or loss/mutation of a tumour suppressor gene (TSG). However, in order for a cell to proliferate abnormally, to de-differentiate to form a malignant clone of cells, to become locally invasive and finally to metastasise, a number of steps are required: rarely would one expect to find a single genetic abnormality within a metastatic cancer, whereas one might do in the case of a small benign tumour (*vide infra*).

The Retinoblastoma Gene and the "Two-hit" Hypothesis

Tumour suppressor genes, also known as antioncogenes, have been appreciated since the early 1970s as a result of the study of patterns of inheritance of the retinoblastoma (Knudson, 1978). This rare tumour occurs either unilaterally or bilaterally in approximately 5/100,000 children; an estimated 40% are hereditary and the remainder are sporadic. The offspring of patients with bilateral tumours, nearly all of whom have a family history of retinoblastoma, have a 95% probability of developing the tumour, either unilaterally or bilaterally. However, only 10 to 15% of unilateral survivors produce affected offspring, mostly unilaterally. Knudson (1978) suggested that a single inherited mutation was not sufficient to produce the tumour and proposed that a second event is required—the so-called "two-hit" hypothesis. In heritable cases, one event is germinal, the other somatic (acquired);

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in non-heritable cases both events would be somatic. The events, taking place at complementary sites on the 2 alleles of the affected chromosome, may be specific mutations such as nucleotide base substitutions, or loss of the normal (wild-type) allele. This theory was given early support by findings of karyotypic abnormalities in 20% of cases, although the more sensitive techniques of linkage analysis and restriction fragment length polymorphism (RFLP) analysis now suggest considerably higher deletion rates. The second event (in whichever form) results in loss of tumour-suppressor function of the wild-type allele.

The retinoblastoma (Rb) gene is located on the long arm of chromosome 13 (13q) in close proximity to the gene encoding esterase D; most retinoblastoma patients have <50% serum esterase D level, implying allele loss in at least that portion of 13q containing the Rb and esterase D genes. In some cases, allele loss in this location is confined to the tumour, both alleles being present in the patient's normal cells; this is proof of somatic mutation (Cavenee *et al.*, 1983). The Rb gene has been cloned and sequenced (Lee *et al.*, 1987); it encodes a protein product which forms complexes with several transforming proteins. In affected cases the mutant gene transcribes abnormal RNA, resulting in an abnormal or absent protein product. Introduction of the wild-type Rb gene into retinoblastoma cell-lines suppresses their malignant phenotype (Huang *et al.*, 1988).

In summary, retinoblastoma is a cancer which provides a model for Knudson's tumour suppressor gene theory: in both hereditary and sporadic forms it is associated with abnormalities of both alleles at a single gene locus; classically one allele is deleted and the other mutated. The protein product interacts with transforming proteins and transfection of the wild-type RB gene suppresses malignant phenotype. The loss of one allele is termed "loss of heterozygosity" (LOH): this is occasionally demonstrated as a gross karyotypic deletion, but if the deletion is small the techniques of Southern blotting/RFLP make use of polymorphic cloned DNA probes applied to paired samples of digested tumour and constitutional DNA. The consistent loss of heterozygosity at a particular locus in tumour DNA may indicate the presence of a tumour suppressor gene and a thorough investigation of the remaining allele may reveal the "second hit".

Other Tumour Suppressor Genes and Candidates

A. The Wilms' Tumour (WT1) gene—*vide infra*.

B. The Neurofibromatosis type 1 (NF 1) gene is a large gene located on the long arm of chromosome 17 (17q) (White, 1992). In affected patients there is allelic deletion or translocation, an inherited hemizygous mutation at the same locus conferring the syndrome of abnormal melanocytes (cafe-au-lait patches), benign neurofibromas and schwannomas. Occasional malignant change is believed to be associated with additional chromosomal loss on the short arm of chromosome 17 (17p), at the p53 locus.

C. The Familial Adenomatosis Polyposis (FAP) gene was mapped by linkage studies to a portion of chromosome 5q, and it has recently been cloned (White, 1992). LOH at 5q occurs in 29% of sporadic adenomas and 35% of carcinomas (Vogelstein *et al.*, 1989). Introduction of wild-type chromosome 5 into colon carcinoma cell lines suppresses the malignant phenotype.

D. The p53 gene is located on chromosome 17p, encompassing 16–20 kilobases (kb). Discovered in 1979, it was initially thought to be an oncogene because its product is present in elevated quantities in transformed cells. The reason for this is that the half-life of the abnormal product is longer than that of the normal. The p53 protein exerts a negative influence on cell growth control, probably by blocking DNA polymerase binding sites in order to prevent DNA replication. Loss of heterozygosity on chromosome 17p occurs in several solid human tumours, including up to 75% of colorectal carcinomas and 30% of breast carcinomas. Nigro *et al.* (1989) demonstrated point mutations within the remaining alleles of such tumours, concentrated in 4 highly conserved regions. This would inevitably result in abnormal RNA and p53 protein synthesis. Transfection experiments have demonstrated suppression of colony forming efficiency of colorectal carcinoma cell lines by wild-type p53 (Baker *et al.*, 1990).

E. The Deleted in Colorectal Carcinoma (DCC) gene is located on chromosome 18q; loss of heterozygosity occurs in over 70% of colorectal carcinomas and 47% of advanced adenomas (Vogelstein *et al.*, 1989). A variety of mutations has also been observed within the remaining allele, resulting in reduced expression of DCC mRNA (Fearon *et al.*, 1990). Somatic genetic changes also occur on chromosome 18q in 38% of 49 primary breast cancers, mostly within the DCC region. The predicted protein product shows sequence homology with neural cell adhesion molecules and related cell surface glycoproteins.

F. The Non-Metastatic "nm23" gene is located near the centromere on chromosome 17p. It was first described in RNA assays of melanoma cell lines, expression being highest in tumours of low metastatic potential and *vice versa* (Steeg *et al.*, 1988). Similar findings were reported in breast cancer, implying that a tumour with high expression is associated with a good prognosis (Bevilacqua *et al.*, 1989). Transfection experiments have confirmed the suppressive effect of nm23 on several aspects of malignancy. The predicted product is similar to a normal transcription factor and its loss may therefore result in destabilisation of cell regulation (Leone *et al.*, 1991a). Loss of heterozygosity at the nm23-H1 locus has been observed in a number of solid tumours, including 64% of breast cancers (Leone *et al.*, 1991b).

G. Molecules of the cadherin and integrin families involved in cell-cell and cell-matrix adhesion are being increasingly implicated in tumour invasion and metastasis. A gene, Cell Adhesion Regulator (CAR), located on chromosome 16q, has been cloned and encodes a protein which enhances such adhesion when transfected into colon cancer cell lines (Pullman and Bodmer, 1992). Another cell adhesion molecule, E-cadherin, is also located on chromosome 16q. Expression is inversely correlated with metastasis in squamous carcinomas of the head and neck and it is implicated as a candidate TSG in a number of other solid tumours, including hepatocellular and gastric carcinomas.

Tumours of the Urinary Tract

It will be clear from the above examples of well studied tumours such as colorectal carcinoma that multiple genetic abnormalities may occur during the malignant process in a particular tumour. Urological cancers are less well understood, although considerable knowledge is being gathered, particularly in the field of Wilms' tumour. Commencing with the kidney and passing distally, current knowledge and theories pertaining to tumour suppressor gene abnormalities in cancers of the urinary tract will be reviewed.

Wilms' Tumour (Nephroblastoma)

Wilms' tumour (nephroblastoma) is an embryonal kidney tumour and is one of the commonest solid tumours of childhood, accounting for about 6% of all paediatric neoplasms. Inherited cases are rare (about 1%), but there are a number of predisposing syndromes which have indicated the existence of putative tumour suppressor genes by their associated chromosomal abnormalities. The commonest of these is the so-called WAGR syndrome, in which Wilms' tumour can occur in children with Aniridia, Genitourinary abnormalities and mental Retardation. These patients often have cytogenetically visible deletions at 11p13, and in sporadic tumours allele loss is seen at 11p in about 50% of cases, indicating the presence of a tumour suppressor gene at 11p13. This gene, WT1, has recently been isolated independently by 2 groups (reviewed by Van Heyningen and Hastie (1992)). The gene covers approximately 50 kb of genomic DNA and codes for a 3 kb mRNA. The polypeptide product is a zinc-finger protein, which has been shown to be able to bind to a specific DNA sequence and to repress the expression of other genes. WT1 is expressed in fetal kidney and a few other sites, indicating that it plays a role in normal genitourinary development. Homozygous deletions, small intragenic deletions and point mutations in WT1 have all been described, including deletions in inherited Wilms' tumours (Pelletier *et al.*, 1991b) and in a Wilms' tumour from a WAGR patient (Brown *et al.*, 1992). Constitutional mutations in WT1 have been detected in 10/10 Drash syndrome patients, in whom male pseudohermaphroditism, glomerulopathy and nephrotic syndrome are accompanied by a high risk of developing Wilms' tumour (Pelletier *et al.*, 1991a). However, the results obtained so far have shown defects of WT1 in only a minority of Wilms' tumours. It is possible that mutations await discovery in parts of the gene not yet examined. Perhaps a more likely explanation is that mutations in other genes are involved in Wilms' tumour, and at least another 2 loci (WT2 and WT3) have been proposed. WT2 has been mapped to 11p15 on the basis of allele loss in some tumours being limited to this region, and the mapping of the Beckwith-Wiedemann syndrome (BWS) locus to 11p15.5. BWS is a fetal overgrowth syndrome which predisposes to several embryonal tumours, including Wilms' tumour. No site has been proposed for the WT3 locus, but its existence is inferred from a few familial cases of dominantly inherited Wilms' tumour in which there is no linkage to any part of 11p. The relative contributions of these genes to Wilms' tumour development awaits their cloning.

Renal cell carcinoma (RCC)

Adenocarcinoma of the kidney constitutes 60% of all renal malignancies and accounts for 2% of all human cancer; it may be inherited or sporadic.

A. Inherited RCC. This type is found in only 1–2% of all cases of RCC. As with other inherited tumours, familial RCC is characterised by earlier age of onset—the mean age at diagnosis is 45 years, more than 15 years earlier than for sporadic cases—and frequent bilaterality and multicentricity. Two groups can be distinguished: pure cases of RCC and cases with von Hippel Lindau (VHL) disease. This latter is inherited in an autosomal dominant fashion and is manifest by retinal, spinal and cerebellar haemangioblastomas, RCC and renal cysts, phaeochromocytomas and other tumours of pancreas, spleen, adrenal glands and liver. Several studies have demonstrated karyotypic abnormalities concerning translocations or deletions of chromosome 3p in cases of pure hereditary RCC and VHL disease. In reviewing these, Maher and Yates (1991) believed that a screening programme for affected families could reduce morbidity and mortality.

B. Sporadic RCC. Cytogenetic and molecular studies have consistently demonstrated chromosome 3p rearrangements at 2 or more loci in up to 90% of cases (Anglard *et al.*, 1982). A gene (designated RIK) that corresponds to the most frequently deleted region is expressed in a variety of human tissues, in particular the kidney. Its expression is markedly reduced in RCC. The product of the RIK gene is believed to be acylpeptide hydrolase, an enzyme that degrades acetylated peptides which include growth factors and regulatory proteins such as bombesin (Erlandsson *et al.*, 1991). In addition, using a technique known as allelotyping whereby paired normal/tumour DNA is multiply probed for loss of heterozygosity, significant deletions have been found on chromosomes 5q, 6q, 10q, 11q, 17p and 19p (Morita *et al.*, 1991). This finding supports the theory that multiple genetic alterations are required during the development of cancers, perhaps beginning in the case of RCC with a loss of genetic material from chromosome 3p. In support of the contention that a candidate TSG exists on 3p, introduction of a normal 3p into a human RCC cell-line resulted in a reduction in growth rate (Shimizu *et al.*, 1990).

Transitional cell carcinoma (TCC) of the bladder

This is the fifth commonest cause of male cancer death in the United Kingdom, although it has a relatively high (64%) 5-year survival rate (Cancer Research Campaign Factsheet, 1989). Early karyotyping revealed frequent (50%) monosomy of chromosome 9 in low grade tumours, but this was not confirmed in subsequent studies on higher grade tumours. Loss of heterozygosity on chromosome 11p was observed in 5 of 12 patients using 2 probes, neither being specific for the WT locus (Fearon *et al.*, 1985). TCC was noted to be the first adult solid tumour to exhibit loss of genes on 11p. Subsequently, DNA from 25 invasive tumours was probed at 9 loci on 9q, 11p, 17p, 14q and 6p (Tsai *et al.*, 1990); allelic losses were recorded on the first 3 of these arms in 67%, 40% (corresponding to the findings of Fearon *et al.* (1985, 1990)) and 63% respectively. p53 mutations have been demonstrated in 11 of the 18 (60%) invasive bladder cancers, strongly associated with chromosome 17p loss (Sidransky *et al.*, 1991). This group also identified p53 mutations in cells obtained from urinary sediment and suggested the possibility of predicting invasive TCC on the basis of finding these mutations in patients' urine samples. Absence of allelic losses on chromosome 17p in 10 low grade 9q- deleted tumours (Olumi *et al.*, 1991) has added weight to this possibility, contributing to a potential multistage model for tumourigenesis of TCC.

Epidemiological evidence has suggested an increased incidence of TCC in retinoblastoma families. Evidence that RB may also be involved in the development of sporadic TCC began with the findings of altered Rb protein or absent Rb mRNA in TCC cell-lines (Horowitz *et al.*, 1989). Further work has provided evidence of Rb abnormalities at a relatively late stage in the natural history of TCC: loss of heterozygosity at the Rb locus has been observed in 28 of 94 tumours (29%), nearly all of which were muscle-invasive (Cairns *et al.*, 1991). However, 44% of invasive tumours studied by this group showed no Rb abnormality and it would be of interest to know the status of the p53 gene in these cases. Presti *et al.* (1991) reported LOH at the DCC locus in 2 of 5 invasive tumours and none of 5 superficial tumours.

In summary, there is a high frequency of chromosome 9q deletion in all grades of TCC, although this has not been reported with other epithelial tumours. The signifiicance of loss of 11p sequences is not clear. RB, DCC and p53 abnormalities appear almost exclusively in high grade invasive tumours and it is likely that multiple abnormalities would be present in the DNA of a metastatic TCC.

Carcinoma of the prostate (CaP)

Adenocarcinoma of the prostate is the second most common cause of cancer death in UK males, accounting for 8230 (10% of the male total) deaths in 1988. From a molecular genetic point of view, this controversial and unpredictable cancer has attracted relatively little interest, although this imbalance is likely to be redressed over the next few years. The Rb gene has received the most attention; an abnormally small Rb mRNA transcript and its protein product have been demonstrated in the CaP cell line DU145 (Bookstein *et al.*, 1990b). Moreover, replacement of the wild-type Rb gene led to reduced tumourigenicity of the cell line in nude mice. Seven human CaPs were similarly analysed (Bookstein *et al.*, 1990a), of which one (metastatic) specimen exhibited loss of heterozygosity at the Rb locus, a deletion of the transcriptional start sites from the remaining allele and resultant absence of Rb-encoded protein.

Looking at 5 CaP cell lines and 2 primary cancers, Isaacs *et al.* (1991) found LOH on 17p at the p53 locus in both primary cancers and 2 cell lines. Sequencing the intact allele revealed point base mutations in 3 of these 4 specimens. A third cell line exhibited 2 alleles, both containing mutations. Further, controlled transfection of wild-type p53 caused growth arrest in 2 of the cell lines. In a case report, Effert *et al.* (1992) described an identical somatic p53 mutation in part of a primary tumour and in a regional lymph node metastasis. In addition, LOH in another region of chromosome 17p was demonstrated only in the metastasis. This evidence points to involvement of a hitherto unidentified TSG on 17p in the metastatic process in this case. The same group found no p53 abnormalities in 9 other primary cancers examined (unpublished).

In search for more common regions of allelic deletion, 2 groups have performed allelotyping studies in human CaP: 24 specimens were probed at 17 sites on 11 chromosomal arms (Carter *et al.*, 1990) and 18 specimens were multiply probed on 45 chromosomal arms (Collins *et al.*, 1991). The first group observed allelic loss on at least one chromosome in 54% of clinically localised tumours and all metastatic tumours studied. Deletions occurred on chromosomes 10q and 16q in 30% of tumours, although other less common deletion sites included areas harbouring candidate TSGs, such as chromosomes 13q, 17p and 18q. The second group also found a high LOH rate on 10q (55%) and 16q (60%), but also striking was the 50% LOH on chromosome 8p. These findings suggest the presence of TSGs, hitherto unknown, on chromosomes 8, 10 and 16. It seems reasonable to speculate that the candidate TSG on 16q is a regulator of cell adhesion (see earlier). In addition, some involvement by the Rb and p53 genes is apparent; the roles of other candidate TSGs in prostatic carcinoma are currently being determined.

Conclusions

The natural history of cancer may be regarded as a multistage process, beginning with dysplasia and ending with metastasis. Each stage in this development is likely to be due to at least one genetic defect, either oncogene activation or loss of a tumour suppressor, so that a metastatic tumour will have multiple such defects. This appears to be the case with the well studied colorectal carcinoma (Vogelstein *et al.*, 1989) and similar patterns are beginning to emerge in the urinary tract cancers. There can be few cancers in which behaviour is less predictable than those faced every day by the urologist. The clinical value of genetic "markers", oncogenes and TSGs, is not yet proven; there is potential for their use as screening tools in cases of familial cancer (for example, hereditary renal carcinoma) and as prognostic indicators. For example, patients with non-metastatic disease may be suitable for conservative treatment if markers known to indicate metastatic potential were absent; on the other hand, a tumour exhibiting multiple genetic abnormalities indicative of metastatic potential may be amenable to curative treatment if it were clinically organ-confined. Management of patients with metastatic disease could also be influenced by such indicators if known: for example, the timing and intensity of androgen deprivation and/or chemotherapy in the treatment of metastatic carcinoma of the prostate in order to obtain the longest remission; perhaps even by reducing unnecessary cost and toxicity.

Our understanding of the molecular biology of these common cancers is in its infancy, but it will broaden with time. To achieve this, close collaboration is essential between clinicians and molecular biologists in order that abnormalities are not only detected but also applied either prospectively or retrospectively to the clinical variables available. Having established which genes play significant roles in each tumour by pilot studies, it may be that large scale, multi-gene investigations will provide us with reliable patterns of progression, applicable to individual cases in order to influence management.

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Surgical Management of Renal Carcinoma with Extensive Involvement of the Vena Cava and Right Atrium

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Summary—Between 1988 and 1990, 8 patients with a renal tumour extending into the vena cava and with supradiaphragmatic extension were treated by an operative technique involving extracorporeal circulation and deep hypothermic circulatory arrest. In 4 patients the thrombus extended into the right atrium. Six patients appeared to have a renal carcinoma. Intra-operatively one patient's tumour proved to be a metastasis of a squamous cell carcinoma of the lung and another patient was found post-operatively to have a leiomyosarcoma of the vena cava. Two of these 6 patients died from metastases 6 weeks and 8 months post-operatively. Four patients are symptom-free, although 3 of them have liver or lung metastases 10, 20 and 37 months post-operatively. One has no evidence of disease 18 months post-operatively.

The use of extracorporeal circulation and deep hypothermic circulatory arrest provides optimal surgical exposure and gives the patients a considerable complaint-free interval post-operatively. How often cure is also achieved is as yet unclear.

A review of the literature shows that tumour extension into the inferior vena cava occurs in 5 to 9% of patients with renal carcinoma (RC). In 20% of these patients the tumour extends into the right atrium and this group presents the greatest problems from a surgical point of view. In the absence of lymph node metastasis, local tumour control is the most important prognostic factor (Clayman *et al.*, 1980; Kearney *et al.*, 1981; Libertino *et al.*, 1987). Extracorporeal circulation (ECC) and deep hypothermic circulatory arrest provide excellent exposure and an extensive renal tumour can be resected safely. We report our experience with patients treated in this way.

Patients and Methods

Eight patients (ranging in age from 48 to 75 years) underwent surgery after radiological examination had confirmed tumour extension and no evidence of lymph node metastases or distant metastases was found. Pre-operative investigations include history, physical examination, laboratory tests—including liver function and coagulation—intravenous urography, ultrasonography of the abdomen, cavography, computed tomography, magnetic resonance imaging and duplex scanning. Four patients with suspected right atrial extension also underwent transoesophageal ultrasonography to evaluate possible tumour fixation in the atrium. All patients were shown to have supradiaphragmatic caval tumour extension and the tumour was examined cytologically.

The procedure began with a median laparotomy to assess the local resectability of the tumour and a final check was made for liver and lymph node metastases. If no metastases were found and the tumour was locally resectable, a radical nephrectomy was carried out, leaving only the renal vein attached to the vena cava. The thoracic surgeons then performed sternotomy and ECC was instituted. The patient was cooled to a nasal temperature of 15°C, the circulation was arrested and the patient exsanguinated. The inferior vena cava and, if

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necessary, the right atrium were opened and the tumour thrombus was removed in a bloodless field (Figs 1 and 2). The cardiovascular and anaesthetic procedures used in these cases have been described by Maat *et al.* (1991).

Results

At laparotomy, one patient's tumour appeared to be too extensive for radical excision. Supplementary frozen section examination revealed a metastasis from a squamous cell carcinoma of the lung which had not been diagnosed by cytological examination elsewhere. In another patient radical surgical intervention was possible only with resection of the vena cava and hemihepatectomy. This patient had an extremely complicated post-operative period and died after 6 weeks. Definitive pathological examination revealed a leiomyosarcoma of the vena cava. In 6 patients resection of a renal carcinoma was performed. In 4 of them extension into the right atrium was found. In 4 patients the primary tumour originated in the right kidney.

Post-operative complications included ischaemic colitis, hypotension and anuria, sepsis, subsequent bleeding and mental problems. Post-operative hospitalisation ranged from 14 days to 4 months. Five of the 6 patients were discharged within 20 days. One patient died after 6 weeks from liver metastases which were not detected either pre-operatively or peri-operatively. One patient died after 8 months from metastases of the RC. Three of the 4 remaining patients are free of symptoms but have recurrent local disease or metastases 10, 20 and 37 months post-operatively. One patient has no evidence of disease 18 months after operation.

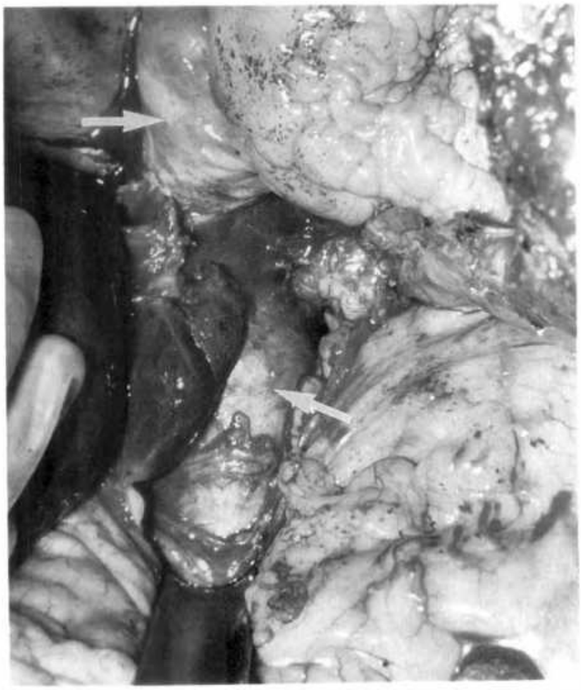

Fig. 1 *In situ* tumour with arrows indicating infradiaphragmatic thrombus.

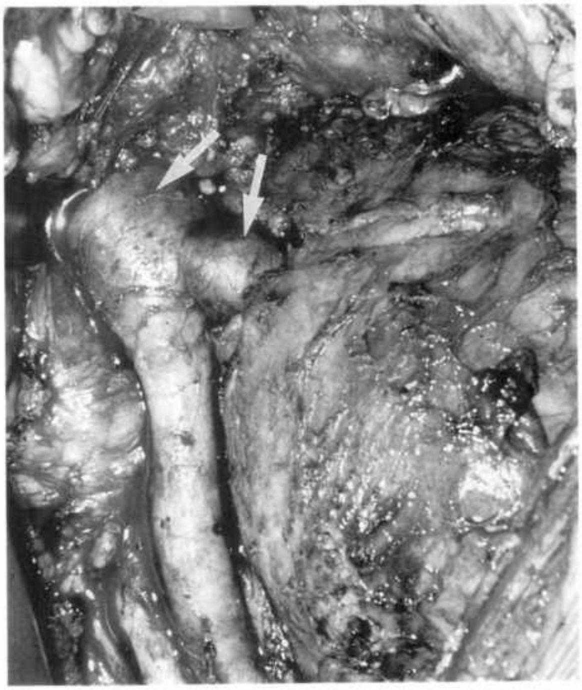

Fig. 2 *In situ* tumour with arrows indicating supradiaphragmatic thrombus and right atrium.

Discussion

In patients with a renal carcinoma and supradiaphragmatic tumour thrombus extension via the vena cava, conventional surgery is often complicated, if possible at all. Operative techniques such as dissection and clamping of the portal vein, the use of a caval-atrial shunt, venous bypass, normothermic circulatory arrest of the lower torso (which is safe for only 20–30 min), catheter thrombectomy and the use of ECC without circulatory arrest may result in serious complications (Scheffť *et al.*, 1978; Cummings *et al.*, 1979; Novick and Cosgrove, 1980; Klein *et al*, 1984; Attwood *et al.*, 1988; Foster *et al.*, 1988). In particular, there is a risk of hypotension at normal temperature, limited exposure and view due to bleeding or liver enlargement, embolisation by parts of the tumour, thrombosis of the lower part of the body, hypoxic liver impairment, acute tubular necrosis and paraplegia.

Circulatory arrest and exsanguination have several advantages. Extended retroperitoneal dissection is not necessary, the surgical field is bloodless and there is a complete overview of the lumen of the inferior vena cava and, if necessary, the right atrium. The risk of fatal blood loss or embolisation of tumour thrombus is strongly reduced. Often there is a knob on top of the tumour thrombus, which prevents easy retraction through the vena cava from the atrium and in these cases it is essential to have the possibility of opening the right atrium, as provided by this technique.

One of the major risks of this technique is subsequent bleeding or even bleeding during the final part of the operation, when the heparinised blood is returned from the cardiopulmonary bypass machine to the patient. To prevent this we are careful to coagulate all structures before cutting them. We also use protamine sulphate to counteract the effect of heparin just after the bypass machine is disconnected.

In only 1 patient did we encounter major haemorrhage that necessitated a second operation on the first post-operative day.

The results obtained in other series, showing apparent cure rates of 9/13 (follow-up 1–33 months) and 4/13 (mean follow-up 30 months), cannot be equalled by our series (Kearney *et al.*, 1981; Montie *et al.*, 1988). Only 1 patient has no evidence of disease 18 months post-operatively. Three patients have no symptoms but do have metastases 10, 20 and 37 months post-operatively. There were no serious complications in the patients with renal carcinoma. The patient with a complicated post-operative course that eventually led to his death appeared not to have had a renal carcinoma but a leiomyosarcoma originating in the inferior vena cava.

Surgical treatment of RC with tumour extension into the right atrium is feasible. The technique described permits excellent exposure and provides an optimal opportunity for complete tumour resection. In some cases a reasonably long symptom-free interval may be obtained. It is not yet clear when cure is possible and what exactly the indications and contraindications of this type of surgery may be.

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Extracorporeal Shock Wave Lithotripsy of Ureteric Stones with the Modulith SL 20

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Summary—A series of 138 patients with ureteric calculi was treated by *in situ* extracorporeal shock wave lithotripsy (ESWL) during the clinical introduction of the Modulith SL 20. This machine represents a newly developed lithotriptor with an electromagnetic cylinder as shock wave source and a dual localisation system consisting of in-line ultrasound and an integrated fluoroscope C-arm. During the first 2 months, 12 patients (phase 1) were treated under ultrasound localisation alone; during the next 5 months, 37 patients (phase 2) were treated using dual imaging modalities with reduced peak pressure (max. 18 kV = 800 bar); during the final 7 months, 89 patients (phase 3) were treated under ultrasonic and fluoroscopic localisation combined with an increased maximal shock wave pressure (20 kV = 1024 bar).

The introduction of fluoroscopic targeting (phases 2 and 3) resulted in satisfactory localisation of calculi in the mid-ureter, previously limited by use of only coaxial ultrasound. The extension of stone localisation to the whole length of the ureter was associated with a marked decrease in treatment time, reflecting the easy handling of the dual localisation system. The rise in generator voltage (phase 3) improved the disintegration rate from 81% (phase 2) to 85%, whereas the number of impulses remained unchanged. However, the rate of auxiliary procedures following ESWL (adjuvant and curative) was reduced from 33% (phase 2) to 24.5%.

Thus the Modulith SL 20 in its final design enables *in situ* ESWL to be the treatment of choice for all ureteric calculi, rendering special positioning techniques or multiple treatment unnecessary.

Previous reports have advocated *in situ* ESWL as the treatment of choice in the management of ureteric calculi (Rassweiler *et al.*, 1986a and b; Graff *et al.*, 1988). This concept is based on the principle of minimal morbidity and invasiveness. In the past, the success of this method has been limited by difficulties in stone localisation, particularly for calculi in the mid-ureter (Cole and Shuttleworth, 1988). The necessity for additional procedures, including ureteroscopy and retrograde stone mobilisation, to achieve stone clearance also underlined the shortcomings of the first and second generation lithotriptors (Simon *et al.*, 1990). In an earlier series, retrograde mobilisation was possible in 80% of cases at the most, resulting in further invasive, curative measures such as retrograde or antegrade ureteroscopy (Alken *et al.*, 1985; Miller *et al.*, 1985). Not only are these adjuvant manoeuvres more invasive—they also carry the risk of septicaemia and ureteric stenosis. Other factors, including total obstruction, stone size and duration of impaction, have been implicated in the failure of *in situ* ureteric ESWL (Rassweiler *et al.*, 1986a and b).

Storz Medical AG (Kreuzlingen, Switzerland) and the Department of Urology, Klinikum Mannheim (Clinical Faculty of the University of Heidelberg, Germany) have developed a new lithotriptor, the Storz Modulith SL 20, aimed at overcoming these limitations (Table 1) (Rassweiler

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Table 1 Criteria for a Third Generation Lithotriptor

I.	X-ray and ultrasonic stone localisation for ESWL of urinary and biliary calculi.
II.	Wide energy range of shock wave source for effective disintegration of difficult stones.
III.	Large aperture focusing system for treatment under minimal analgesia.
IV	Fluoroscopic table allowing multifunctional use of the lithotriptor.
V.	Low cost and maintenance.

et al., 1990a). This advanced lithotriptor has enabled us to re-evaluate the question of *in situ* ESWL for all ureteric calculi and, in particular, to determine whether the combination of imaging techniques and higher shock wave energy will improve on our previous experience.

Materials and Methods

Technical data

In the Modulith SL 20 the shock wave source consists of an electromagnetic cylinder containing an in-line ultrasound scanner. The shock front is focused by a parabolic metal reflector with a diameter of 30 cm. The focal size is 6 × 28 mm (at 15 kV). Fluoroscopic localisation is provided by the integrated C-arm (Table 2).

Table 2 Modulith—Shock Wave Generator

Shock wave source	*Electromagnetic cylinder*
Range	12–20 kV (190–1200 bar)
Focusing	Paraboloid reflector
Aperture (cm)	30
Focal size (mm)	6 × 28
Focal depth (cm)	2–15

Stone localisation

Ultrasonic localisation was employed for upper and pre-vesical ureteric calculi with the patient in either the supine-oblique (upper third) or the prone-flat position.

Fluoroscopic localisation was primarily used for all other ureteric stones with the patient in either the supine-flat (upper third) or prone-flat (mid and distal ureter) position. The patient is manoeuvred under the integrated C-arm and then centred in the virtual focus (F_v). He/she is then manually manoeuvred back on to the shock wave source and the water cushion is carefully coupled without moving the patient (Fig. 1). In approximately 20% of these cases the stone can be visualised by an in-line ultrasound and thus monitored during treatment. In the remainder, fluoroscopy is carried out after 400 shocks and then after 500–1000 impulses, depending on the stability of the patient's position. It must be emphasised that this stability is ensured by the integrated "acoustic cradle" consisting of an impedance-adapted foil (Fig. 2).

Patients and indications

Between August 1989 and December 1990, 138 patients with ureteric calculi were treated by 1 of 3 therapeutic protocols (phase 1, 2 or 3). Allocation depended on the time of presentation during the study and *in situ* ESWL was performed regardless of stone size or duration of obstruction.

Phase 1. This 2-month study involved the first 12 patients treated on the prototype Modulith SL 10, incorporating coaxial ultrasound as the only means of stone localisation. The maximum generator voltage was 18 kV, corresponding to a peak pressure of 800 bar (PVDF-hydrophone, Imotec).

Phase 2. The next stage of the study, which lasted for 5 months, involved 37 patients treated on the upgraded Modulith SL 20. This incorporated the dual imaging modalities of coaxial ultrasound and fluoroscopic stone localisation. The concept was to provide a total imaging system with respect to all ureteric calculi. The maximum generator voltage in this series remained the same (18 kV).

Phase 3. The final 7 months of the study involved 89 patients treated on the Modulith SL 20, which was subject to further modification. The shock wave energy was increased to 20 kV (corresponding to a peak pressure of 1024 bar), with the aim of improving disintegration without causing additional pain.

Statistically, there was no significant difference between the various treatment groups with respect to stone distribution, stone size or duration of obstruction (Table 3).

In all 3 phases the patients were treated with a standard regimen of analgesia: 3.5–7.5 mg piritramide (Dipidolor®) intravenously plus 5–10 mg midazolam (Dormicum®) if necessary.

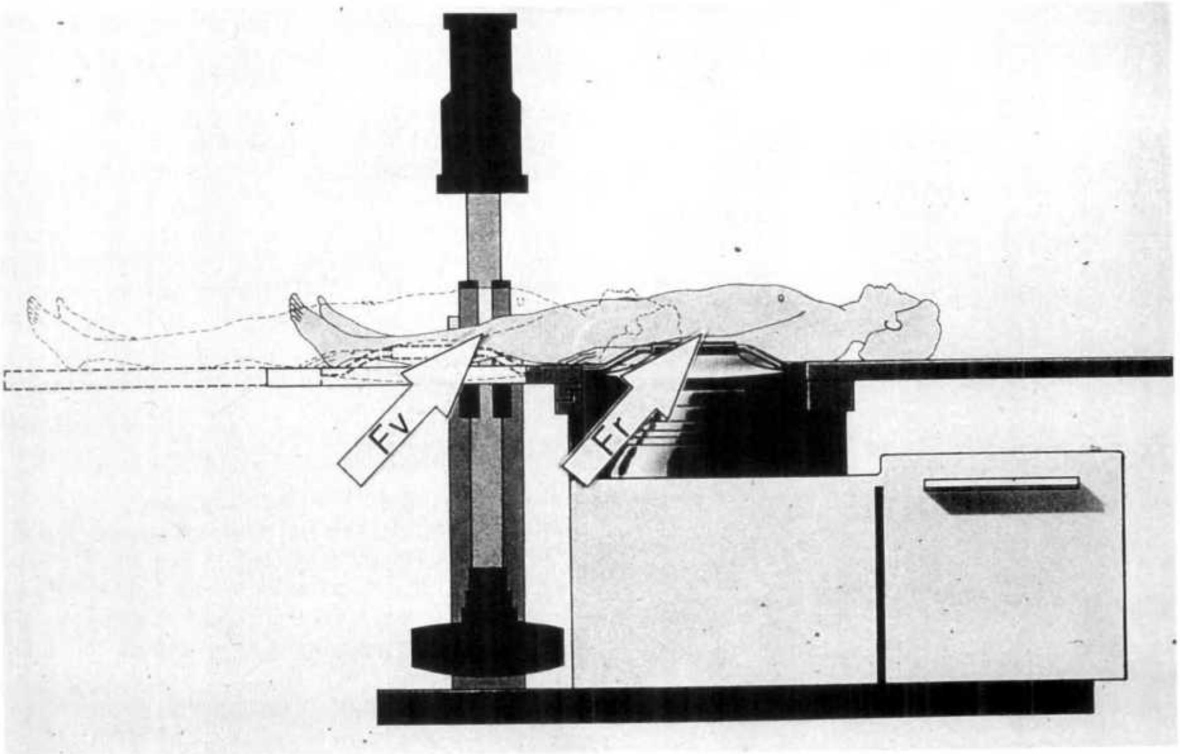

Fig. 1 Storz Modulith SL 20. Fluoroscopic stone localisation. Shift from real focus (in-line ultrasound) into virtual focus F_v. After fluoroscopic stone localisation, mechanical return to treatment position and careful coupling with flat position of the water cushion.

Table 3 Ureteric Stone Distribution

Phase		*1*	*2*	*3*
No. of patients		12	37	89
No. of stones		12	37	91
Site:	Upper (%)	67	50	56
	Middle (%)	—	7	16
	Lower (%)	33	43	28
Size:	<1 cm (%)	67	75	66
	>1 cm (%)	33	25	34

Table 4 Auxiliary Procedures

Curative	*Adjuvant*
Loop extraction	Retrograde mobilisation
Ureteroscopy	Percutaneous nephrostomy
Laser lithotripsy	Stent

Successful *in situ* ESWL was defined as complete disintegration of the calculus in 1 or 2 sessions without the need for auxiliary measures due to incomplete fragmentation. Auxiliary measures were categorised as curative or adjuvant (Table 4). Curative procedures were defined as measures undertaken to achieve stone clearance after incomplete fragmentation (mainly ureteroscopic stone extraction). Ureterorenoscopy (URS) is often performed under analgesic sedation, but general anaesthesia may become necessary, particularly in male patients. Adjuvant intervention, either before or after ESWL, involved minor procedures to prevent or resolve the complications of *in situ* treatment. These were performed either without or under mild anaesthesia.

This study had 2 aims with respect to the Storz Modulith SL 20.

1. Does the combination of a combined targeting system lead to satisfactory stone localisation of all ureteric calculi?
2. Does increasing the shock wave energy (kV) improve the efficacy of the lithotriptor with a consequent reduction in invasive auxiliary procedures to achieve stone clearance?

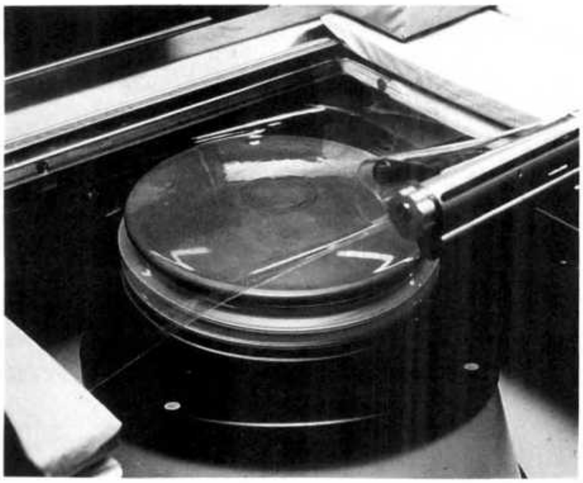

Fig. 2 Stable position of the patient during shifting by means of the "acoustic cradle".

Results

In all, 138 patients were treated by *in situ* ESWL with a stone distribution listed in Table 3. The absence of stones in the mid-ureter in the phase 1 study reflects the limitations of localisation using coaxial ultrasound alone. The introduction of a fluoroscopic targeting system for phases 2 and 3 resulted in satisfactory localisation of calculi in the mid-ureter, previously described as "nowhere land" (Eisenberger *et al.*, 1985; Chaussy, 1988). Thus, a dual imaging system combining X-ray and ultrasound provided suitable access to the whole of the ureter and achieved the first aim of the study.

Treatment data for the 3 phases of the study are listed in Tables 5 and 6. There was no significant difference with respect to the number of shock waves for each phase, but there was a marked decrease in treatment time. The initial time difference between phases 1 and 2 reflects our learning curve with the Modulith, but the further reduction in treatment time in phase 3 coincided with an increase in shock wave energy (kV) and reflects the easy handling of the combined localisation system.

Table 5 Ureteric Stones: ESWL Data

Phase	*1*	*2*	*3*
No. of treatments/patients	1.16	1.06	1.15
No. of shock waves	2423	2875	2895
Generator voltage (kV)	17.7	17.7	19.3
Mean treatment time (min)	80	59	38

Table 6 Results of Treatment after 5 Months

Phase	*2*	*3*
Disintegration rate (%)	81	85
Retreatment rate (%)	6	14
Stone-free (%)	82	90
Remnants < 5 mm (%)	11	2.5
Remnants > 5 mm (%)	7	7.5

Table 7 Auxiliary Procedures

Phase		*2 (%)*	*3 (%)*
Curative			
Loop extraction		8	6
Ureteroscopy		10	9
PCNL*		1	—
Adjuvant			
Before:	Retrograde mobilisation	3	2.5
	Stent	11	7
	PCNL	3	3
After:	Stent	14	5
	URS	—	4.5
Total		39†	31‡

* PCNL: percutaneous nephrolithotomy.

† 11% of patients underwent pre- and post-ESWL auxiliary measures.

‡ 6% of patients underwent pre- and post-ESWL auxiliary measures.

Consequently, the increase in generator voltage was seen to improve the disintegration rate of ureteric calculi in phase 3 (81 to 85%). The success of this higher disintegration level reduced the complication rate for *in situ* ESWL, as demonstrated by the reduced number of curative and adjuvant interventional procedures performed after ESWL in phase 3 (24.5 *vs* 33%) (Table 7). Curative measures were mainly URS and the post-ESWL adjuvant measures comprised placement of an indwelling stent in the vast majority of cases. It should be noted that 11% of patients in phase 2 and 6% of patients in phase 3 underwent additional auxiliary procedures before and after ESWL.

The cost of this reduction in post-ESWL adjuvant measures is reflected in the higher retreatment rate in phase 3 (14 *vs* 6%). Despite the department's acquisition of a pulsed dye laser, the rate of curative procedures remained unchanged.

These results confirm that a combination of targeting systems with a high shock wave energy increases both the disintegration rate and improves the overall success rate of *in situ* ureteric ESWL.

Discussion

Previous experience with *in situ* ESWL for ureteric calculi was associated with disappointing initial success rates of 60 to 62% (Alken *et al.*, 1985; Miller *et al.*, 1985). Improved focusing and positioning techniques increased the success rate to 75% with the Dornier HM3 (Rassweiler *et al.*, 1986a and b; Graff *et al.*, 1988). Retrograde mobilisation, whenever possible, resulted in a 95% disintegration rate and this method became routine in several centres (Alken *et al.*, 1985; Lingeman *et al.*, 1986). Experimental work by Müller *et al.* (1986) implicated some important factors in the failure of *in situ* ESWL. It was proposed that the main cause of failure was the lack of a suitable interphase between the calculus and urine to allow expansion of fragments. Other important difficulties with *in situ* treatment involved localisation of the ureteric calculus and attenuation of shock wave energy on stone impaction (Rassweiler *et al.*, 1986a and b). The stones in the various treatment groups in the present study did not differ with respect to these criteria (Table 3).

The development of the Modulith was undertaken with the following characteristics in mind: (1) Fluoroscopic and ultrasonic localisation to permit ESWL of all urinary and biliary calculi; (2) wide energy range of shock wave source for effective disintegration of difficult stones; (3) large aperture focusing system to permit treatment under intravenous analgesia; (4) multifunctional use of the lithotriptor table; (5) low cost and maintenance (Rassweiler *et al.*, 1990a). Such characteristics may define a so-called "third generation lithotriptor" (Table 1). *In vitro* measurements and *in vivo* animal trials, using the prototype Modulith, demonstrated that the wide range of energy source and the generator voltage was safe for clinical lithotripsy (Rassweiler *et al.*, 1988, 1990a). The preliminary results were promising in the treatment of urinary and biliary calculi (Henkel *et al.*, unpublished data).

Ultrasonic stone localisation systems, as used in most of the second generation lithotriptors, limit the overall success rate of *in situ* treatment of ureteric calculi to 42% (Rassweiler *et al.*, 1990b; Schmidt *et al.*, 1990). These are generally calculi in the upper third of a dilated ureter or situated in the distal intramural portion. Fluoroscopic localisation, in contrast, localises more than 80% of ureteric calculi, but there is still the area over the iliac ureter. Previously, this was also considered "nowhere land" for *in situ* ESWL (Eisenberger *et al.*, 1985; Chaussy, 1988). The combination of a dual targeting system in phase 2 of this study, with ESWL in the prone position for calculi over the sacroiliac joint (Miller and Hautmann, 1987; Jenkins and Gillenwater, 1988), demonstrates that all ureteric calculi are now suitable for *in situ* ESWL. For the treatment of mid or distal ureteric stones it should be noted that, unlike the Dornier HM3, no special positioning technique (Rassweiler *et al.*, 1986a and b; Miller and Hautmann, 1987; Cole and Shuttleworth, 1988; Jenkins and Gillenwater, 1988; Miller *et al.*, 1988) is necessary on the Modulith SL 20.

In situ treatment of ureteric calculi is usually performed in the upper range of shock wave energy to achieve satisfactory disintegration. Any attenuation of the shock wave (in order to reduce pain) decreases the disintegration rate and increases the number of retreatment or auxiliary procedures required to achieve complete stone clearance. Neisius *et al* (1991) reported that all of their ureteric calculi had to be treated twice on the Piezolith 2500, which is also fitted with a dual localisation system. Increasing the generator voltage, as in phase 3 of the present study, could theoretically render the treatment unacceptable under intravenous analgesia because of increased pain. Our results show that a shock wave energy of 20 kV (corresponding to a rise in peak pressure from 800 to 1024 bar) improved the disintegration rate with no adverse effect on the patient's perception of pain. Presumably this is a result of the wide aperture focusing system on the Modulith. Thus there is no significant change in the focal zone and focal depth after increasing the maximum generator voltage. The rise in generator voltage has also reduced the number of post-ESWL adjuvant procedures, which indicates improved fragmentation. Although this involved an increase of 8% in the retreatment rate, it is a small price to pay considering the fact that further intervention, especially in the male, often requires general anaesthesia and carries a risk of further morbidity (Carter *et al.*, 1986; Coptcoat *et al.*, 1987; Miller *et al.*, 1988). However, it must be noted that the introduction of miniscopes as well as lasertripsy has minimised these risks (Watson *et al.*, 1987; Rassweiler *et al.*, 1991). For this reason, we performed most of our remaining "curative" ureteroscopies in phase 3 (Table 7) with the patient under analgesic sedation, using a new dye laser with a stone-detection device (Rassweiler *et al.*, 1992).

The results of this study confirm the efficacy of the dual localisation concept of the Modulith SL 20 for the treatment of *all* ureteric calculi. The rise in generator voltage further improves the success rate of *in situ* ESWL.

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Extracorporeal Lithotripsy of Ureteric Calculi Using the Dornier HM-3 Lithotriptor

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Summary—Over a 5-year period (November 1984–November 1989), we treated 356 patients with ureteric calculi; 170 were treated by extracorporeal shock wave lithotripsy (ESWL) on a Dornier HM-3 lithotriptor. The calculi (n = 176) were uniformly distributed along the length of the ureter: 44 were just below the pelviureteric junction, 59 were lumbo-iliac, 42 were in the upper bony pelvis and 32 in the lower bony pelvis. The mean diameter of the upper ureteric calculi was 10 mm and for the others it was 8 mm. Thirty-four patients with acute obstructive pyelonephritis required pre-ESWL drainage of the urine. X-ray localisation required intraveneous urography during lithotripsy in 52 cases (30%). On plain X-ray the following day 170 stones (96%) were judged to have disintegrated. The 6 patients whose stones were not fragmented received further treatment (ureterotomy (4) and ureteroscopy (2)). Five patients required additional treatment because of pain or fever (catheterisation (3) and ureterotomy (2)) and 2 patients had a second lithotripsy owing to insufficient fragmentation. Four patients were lost to follow-up.

In 153 patients (90%) the fragments were eliminated completely, 146 in the first month and the remainder before the sixth month. No serious sequelae were observed. In addition to the 5 patients who required supplementary treatment. 11 patients with pain or fever needed medical treatment. We recommend first intention *in situ* ESWL for all ureteric calculi.

The aim of this study was to demonstrate the possibility of treating virtually all ureteric calculi by ESWL. Such calculi were initially excluded from ESWL by Chaussy *et al.* (1980, 1982). Miller *et al.* (1985) published the first report of success with upper ureteric calculi.

Patients and Methods

In France, the first ureteric calculi were treated at the Centre Inter Etablissements de Lithotriptie of the Assistance Publique de Paris in 1984. From November 1984 to November 1989, using the Dornier HM-3 lithotriptor with X-ray localisation, 176 ureteric calculi were treated by ESWL. The study group included 170 patients (134 men and 36 women) whose mean age was 40 years (range 7–84). Two patients underwent 2 consecutive ESWL sessions, so that the total number of treatments was 172 for 170 patients. Six patients had 2 ureteric calculi, making a total of 176 calculi in 170 patients. The distribution of the stones according to size and location is shown in the Table.

Before treatment all patients underwent intravenous urography (IVU), urine analysis, blood count and coagulation tests. Plain X-rays of the abdomen, AP and lateral, were done immediately before lithotripsy. In 34 patients, acute obstructive pyelonephritis required prior drainage of the urine

Table Distribution of Calculi According to Position

Size (mm)	*Upper ureter*	*Lumbo-iliac*	*Upper pelvic*	*Lower pelvic*
<5	0	9	9	8
5–10	33	44	27	17
10–15	6	5	4	5
>15	5	1	2	1
Distribution	44 (25%)	59 (33%)	42 (24%)	31 (18%)

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(32 times by a ureteric catheter alongside the calculus and twice by percutaneous nephrostomy).

Regardless of the position of the calculus, its initial localisation was attempted in the conventional half-sitting position. If the localisation time approached 605 without having found the stone, the patient's position was changed and an IVU was obtained. Some iliac calculi were localised in the prone position and pelvic calculi that were unidentifiable in the outstretched position were localised in the seated position. The lack of visibility of the calculus was sometimes overcome by performing an IVU during localisation (52 times; 30% of the cases).

Before 1989 it was necessary to use general anaesthesia 43 times, epidural anaesthesia 78 times and sedation 17 times to supplement premedication. Of 74 treatments carried out since 1989, no general anaesthesia was required, but 16 patients had epidural anaesthesia, 26 sedation as well as premedication, and 32 had premedication alone. The number of shock waves per calculus ranged from 2000 to 4000.

Lithotripsy was terminated on the basis of an impression of a change in the contour of the texture of the X-ray image of the calculus rather than the certainty of disintegration proved by the dispersion of sand.

The urine was usually haematuric after lithotripsy: in addition, 11 patients complained of lumbar pain and 5 had a fever (<38.5°C). Antispasmodic and anti-inflammatory treatment was prescribed 11 times. Antibiotics were given only to pyuric and bacteriuric patients. A plain X-ray of the abdomen was taken on the following day to assess fragmentation. If fragmentation appeared satisfactory, follow-up was confined to plain X-ray, cytobacteriological urine analysis and renal echography 8 and 45 days later.

Results

Patients who eliminated their stones completely were considered cured. The absence of fragmentation indicated failure and fragmentation with incomplete elimination indicated residual calculi.

On the plain X-ray taken 24 h after treatment, 170/176 calculi were fragmented (96%).

Of the 6 patients (3.5%) whose stones were not fragmented, 4 were treated by ureterotomy and 2 by ureteroscopy. Seven patients (4%) received supplementary treatment because of pain or fever, although the calculus was fragmented: ureterotomy (2 patients), catheterisation (3) and repeat ESWL (2) for inadequate fragmentation. Four patients could no longer be contacted.

Thus 166 patients with 172 ureteric calculi were assessed.

A total of 153 patients (92%) eliminated their fragments completely (146 (88%) in the first month and 7 (4%) before the sixth month).

The 6 immediate failures have been discussed. Of the remaining 166 calculi, 159 were eliminated without supplementary treatment (92.5%). Seven required supplementary treatment. In all, 164/172 calculi were eliminated without surgery or ureteroscopy (95.3%).

Discussion

Of 356 ureteric calculi treated between 1984 and 1989, 176 were treated by ESWL, 149 by open ureterotomy and 31 by ureteroscopic extraction. The percentage treated by ESWL rose steadily (Fig.). Thus in 1989, 70/74 ureteric calculi (94.5%) were destroyed by ESWL and the remaining 4 removed by ureterotomy.

For sub-pelvic, upper lumbar and lower pelvic calculi, regardless of the method of localisation, success rates of over 85% have been reported. When lithotriptors with ultrasound localisation were used, success rates ranged from 79 to 86.5% (unpublished material). For lithotriptors with X-ray localisation the success rate was 90% (Coptcoat *et al.*, 1987; Lingeman *et al.*, 1987; Fetner *et al.*, 1988; Graff *et al.*, 1988; Ikemoto *et al.*, 1988; Lupu *et al.*, 1988; Chatelain *et al.*, 1990). Calculi in these sites are extremely amenable to lithotripsy, especially if localised by X-ray.

For lumbo-iliac and upper pelvic calculi, ultrasound localisation produced poor results (<50%

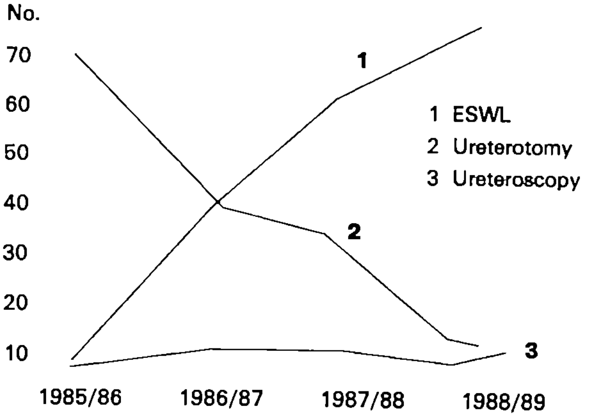

Fig. Treatment of ureteric calculi at Hôpital Necker.

success rate for the former and 65% for the latter) (unpublished material).

Our localisation problems were overcome by intravenous urography (52 times) during lithotripsy, combined if necessary with a change in the patient's position.

For lumbar calculi, Fetner *et al.* (1988) reported 138 patients (83%) cured 6 weeks after *in situ* ESWL without catheterisation. Our results are similar, with an 85% success rate in 1 month.

For iliac calculi, 2 problems had to be overcome: interruption of the shock wave by the iliac bones and the sacrum when the waves penetrate from behind, and the ability to localise a stone positioned far in front of the focus F2 of the ellipsoid of revolution.

Jenkins and Gillenwater (1988) and Tiselius *et al.* (1988) were the first to suggest lithotripsy in the prone position, except for sexually active women because of the risk of irradiating the ovary. Iliac localisation led to a success rate of 90% at 6 months. Jenkins and Gillenwater (1988) and Tiselius *et al.* (1988) reported success rates of 93 and 87.5% respectively. These good results can be ascribed to X-ray localisation. This zone is invisible to those using ultrasound localisation.

For upper pelvic calculi, opinions vary. Some authors feel that pelvic stones are amenable to ureteroscopic extraction (Coptcoat *et al.*, 1987; Ikemoto *et al.*, 1988; Zerbib *et al.*, 1990), but we believe it is simpler to use ESWL first.

In the present series, 42 upper pelvic calculi were treated *in situ* without endoscopic manipulation, with a 93% success rate after 1 month. Chatelain *et al.* (1990) reported a success rate of 98%.

Two calculi that were superimposed on the transverse process of L5 could not be localised despite using all of the methods described above and they were treated by ureterotomy. Four calculi (2 pelvic, 1 lumbar and 1 sub-pelvic) underwent ESWL without fragmentation. The absence of post-ESWL haematuria in these patients leads us to believe that the shock waves were not focused on the urinary tract. Two patients underwent ureterotomy and 2 ureteroscopy.

A success rate of 96.5% at 6 months justifies our claim that *in situ* ESWL with an X-ray localisation lithotriptor is an excellent method for treating radio-opaque ureteric calculi, irrespective of their position.

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Proteinuria and Enzymuria in Vesicoureteric Reflux

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Summary—Vesicoureteric reflux is a common abnormality of the urinary tract leading to significant renal morbidity and premature mortality. No reliable non-invasive method exists for its diagnosis. This study investigated the presence of urinary proteins and enzymes in healthy children and those with reflux. A log normal distribution was found for all analyte/creatinine ratios. Significantly higher tubular protein/creatinine ratios were found in patients with reflux nephropathy. Three enzyme/creatinine ratios (n-acetyl-B-D-glucosaminidase, gamma-glutamyl transferase and lactate dehydrogenase) were higher in children with reflux who had no renal scarring, but the degree of overlap with the normal range was such that it is doubtful whether any will be of use as a urinary marker.

Vesicoureteric reflux (reflux) is a common abnormality of the urinary tract and occurs in approximately 1 in 250 live births (Hodson, 1978). The renal damage (reflux nephropathy) which may result from a combination of reflux and infection accounts for 24% of all cases of end-stage renal failure in children and young adults (Broyer *et al.*, 1985). Nine of 10 cases of severe hypertension in this age group have a renal cause (De Swiet and Dillon, 1989) and in over 50% this is found to be reflux nephropathy (Londe, 1978). The current method of diagnosis (micturating cystourethrography (MCU)) is invasive and an unsuitable screening method for this common disorder. Although there have been considerable advances in ultrasound and radioisotope techniques, a reliable non-invasive method of diagnosis is still elusive.

Heavy proteinuria implies advanced glomerular damage and is a sinister indication of worsening renal function (Kincaid-Smith and Becker, 1978). In a follow-up series (Bailey, 1984), all children deteriorating to end-stage renal failure excreted more than 0.5 g urinary albumin per day at first presentation. The presence of a small loss of albumin ("microalbuminuria") is a reliable indicator of progression of renal disease in diabetes (Gibb *et al.*, 1989) and hypertension (Losito *et al.*, 1988). Although it is now well established that heavy albuminuria means a poor prognosis in advanced reflux nephropathy, little information is available on its significance in the early stages of the disease.

Histological evidence suggests that a marker of tubular damage or dysfunction should be more sensitive in the diagnosis of early nephropathy (Heptinstall and Hodson, 1984). There is additional physiological evidence, in studies of concentrating ability, that reflux causes a reversible tubular injury (Uehling and Wear, 1976; Mundy *et al.*, 1981). In tubular disease the protein present in urine is a smaller size than albumin (Hardwicke *et al.*, 1970) and could therefore provide clues to the site of damage.

Urinary beta$_2$ microglobulin (B_2M) has been used as a marker of damage in tubular disorders, and heavy metal or aminoglycoside toxicity (Schardijn and Van Eps, 1987; Karlsson *et al.*, 1980), but it has the particular problem of deteriorating in acid urine (Hardwicke, 1984). Alternatives include alpha$_1$ microglobulin (A_1M) and retinol binding protein (RBP). Their sensitivity is similar to that of B_2M and they are more stable in acid urine (Bernard *et al.*, 1982; Yu *et al.*, 1983).

Over 30 enzymes have been found in the urine (Mattenheimer, 1971). Most urinary enzymes originate from various parts of the renal tubular cell and its luminal brush border (Grotsch and Matten-

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heimer, 1983). A selection has been chosen since reflux may damage particular parts of the renal tubular cells. N-acetyl-B-D-glucosaminidase (NAG) is predominantly lysosomal, while lactate dehydrogenase (LDH) is found in the cytoplasm. Alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and alanine aminopeptidase (AAP) are bound to the brush border membrane and are thought to have reabsorptive functions (Guder and Ross, 1984). High urinary enzyme activity is usually indicative of parenchymal damage, although micro-organisms and white blood cells can increase the apparent activity. Urinary enzymes have been studied particularly in drug and heavy metal toxicity (Price, 1982) and renal transplant rejection (Wellwood *et al.*, 1975).

The purpose of this study was to document concentrations of a range of urinary proteins and enzymes, from both healthy and affected children, in order to establish whether any may be useful in the early diagnosis of reflux.

Patients and Methods

Urine was collected from babies and children using the Hollister U-bag or clean catch techniques. In the control group were children of colleagues, those attending toddler and play groups, and some having minor surgical operations. None had a history of urinary symptoms. Babies were recruited from the local maternity hospital and a "well baby" clinic; all had a normal prenatal ultrasound scan.

Children in the study groups presented with either urinary tract infection or an abnormal prenatal ultrasound scan. Reflux was shown on subsequent MCU and renal scarring documented by ^{99m}Tc dimercaptosuccinic acid (DMSA) scanning or intravenous urography. Children with significant renal impairment (serum creatinine >125 μmol/L) were excluded from the study. The 3 groups studied were controls, children with reflux whose kidneys were normal and children with reflux and renal scarring.

Urine was collected into a sterile universal container and processed within a few hours of collection. An aliquot was sent for microscopy and culture and the specimen was rejected if >50 white cells were seen or $>10^5$ organisms per ml of urine were cultured.

Samples for albumin were mixed with azide (0.1% w/v) and stored at 4°C. Samples for tubular proteins and NAG were neutralised and stored at −20°C; those to be analysed for the other enzymes were neutralised and mixed with glycerol before storage at −20°C (Maruhn *et al.*, 1986).

Creatinine was assayed by the Jaffé method (Henry, 1974) on a Monarch centrifugal analyser (Instrumentation Laboratory, Lexington, USA).

Albumin was measured by an immunoturbidimetric method on a Monarch centrifugal analyser, with antiserum obtained from Atlantic Antibodies (Incstar Ltd, Winnersh). A range of standards was prepared from human serum albumin (Behring Diagnostics, Hounslow).

A_1M was assayed by rocket immunoelectrophoresis (Laurell, 1975) with antiserum obtained from Dako Ltd, High Wycombe. Standards were kindly provided by Dr R. Chambers, Bristol.

Retinol binding protein (RBP) was measured by radioimmunoassay, according to the method described by Beetham *et al.* (1985), using standards and reagents purchased from St Bartholomew's Hospital, London.

Urinary enzymes were measured on a Monarch centrifugal analyser at 37°C.

N-acetyl-B-D-glucosaminidase (NAG, E.C. 3.2.1.30) was determined by means of a colorimetric procedure using 2-methoxy-4-(2′-nitrovinyl)-phenyl-2-acetamido-2-deoxy-B-D-glucopyranoside as substrate, previously described by Yuen *et al.* (1984). NAG test kits and calibrators were purchased from Cortecs Ltd, Deeside.

Aliquots for other enzyme analyses were applied to columns pre-packed with Sephadex G25 (Pharmacia Ltd, Milton Keynes) to remove small molecular weight inhibitors as described by Grotsch and Mattenheimer (1983).

Lactate dehydrogenase (LDH, E.C. 1.1.1.27) was measured using the reverse reaction of pyruvate to lactate under Scandinavian conditions (Keiding *et al.*, 1974); NADH was purchased from Sigma Chemical Company, Poole, and pyruvate from BDH Chemicals Ltd, Poole.

Alanine aminopeptidase (AAP, E.C. 3.4.11.2) was measured using an optimised kinetic assay with alanine-4-nitroanilide as substrate (Sigma Chemical Company), as described by Jung and Scholz (1980).

Alkaline phosphatase (ALP, E.C. 3.1.3.1) was assayed using p-nitrophenylphosphate substrate in 2-amino-methyl-propan-1-ol buffer, pH 10.3, as described by Tietz *et al.* (1980). ALP kits were purchased from Boehringer Mannheim (Mannheim, Germany).

Gamma-glutamyl transferase (GGT, E.C. 2.3.2.2) was measured using the substrate L-gamma-glutamyl-3-carboxyl-4-nitroanilide, according to the method of Persijn and van der Slik (1976), and reagents were purchased from Boehringer Mannheim.

Results were expressed as the concentration of protein or activity of enzyme divided by the urinary creatinine. Enzyme activity was expressed as IU/mmol creatinine where a unit is equivalent to 1 μmol chromophore released per min.

Results

Normal ranges were calculated from urine protein and enzyme/creatinine ratios found in healthy children (Table 1); 193 control specimens were analysed but several dilute specimens with low creatinine values (<1 mmol/L) and/or undetectable analyte concentration were omitted from the statistical analysis. Correlation between urinary creatinine concentration and urine flow rate is known to be poor when the urinary output is high (Price, 1978) and studies have shown that urinary enzyme output is related to diuresis (Raab, 1972; Jung and Schulze, 1986).

The results were initially divided into 2 age groups (0–30 and 30–120 months) and the distributions statistically examined using the chi-squared normality test. The distributions were found to be log-normal for all analytes and not Gaussian.

Student's *t* test, after log transformation of the results, was used for all of the following statistical analyses. There was no statistical difference between the sexes for any of the analytes measured; for example, Figure 1 shows the variation of the AAP/creatinine ratio against age for boys and girls.

Normal ranges for the analyte/creatinine ratios are shown in Table 2. Variation with age was examined by dividing the control group into 6 cohorts (0–2.9, 3–11.9, 12–23.9, 24–35.9, 36–59.9 and 60–120 months). In general, all analyte ratios decreased with the increasing age of the child (for example AAP in Fig. 1). The rate at which this occurred enabled varying age groups to be combined for each analyte. Patient and control groups were compared where sufficient patient numbers existed within any particular age group.

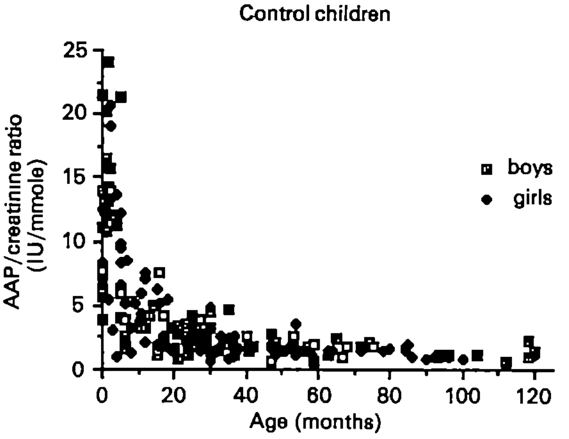

Fig. 1 Influence of age and sex on urinary alanine aminopeptidase/creatinine ratio.

Significant differences between the groups for all analytes studied are shown in Table 3. Few babies and very young children with reflux were seen during the study, but sufficient patients in the older age groups were available for analysis. Children with reflux but no scarring had higher LDH, GGT and NAG ratios in certain age groups, but there was considerable overlap for all analytes such that conclusions could not easily be drawn from any individual result of analyte/creatinine ratio. In children with reflux and scarring, all analyte ratios apart from ALP, LDH and GGT were significantly higher in certain age groups. The most marked differences in the mean values were seen with the tubular proteins A_1M and RBP, but Figure 2 (RBP) shows the considerable overlap with controls.

Discussion

We found a log distribution for all analyte ratios. This has been described for NAG by Osborne (1980) and Watts *et al.* (1988), for ALP and LDH

Table 1 Details of Patients

	Boys	*Girls*	*Total*	*Age range*	*Mean age (months)*
Controls	101	92	193	1d–120 m	34
Reflux	23	41	64	3d–120 m	48
Reflux with scarring	20	24	44	5d–120 m	57

d = day. m = month.

Table 2 Urinary Analyte/Creatinine Ratios in Normal Children. (The mean and 95% confidence limits were calculated from the logarithm of the observed values)

a. Albumin/creatinine ratios

Age (months)	*No*	*Mean (mg/mmol)*	*95% confidence limits (mg/mmol)*
0–2.9	19	6.4	0.1–33.6
3–11.9	19	2.4	0.7–9.0
12–23.9	21	2.4	0.5–12.5
24–35.9	20	1 3	0.3–6.3
36–59.9	32	0.9	0.3–3.1
60–120	33	1.0	0.2–4.3

b. Alpha$_1$ microglobulin/creatinine ratios

Age (months)	*No.*	*Mean (mg/mmol)*	*95% confidence limits (mg/mmol)*
0–2.9	19	4.9	1.0–25.2
3–11.9	18	0.9	0.4–2.0
12–23.9	19	0.8	0.2–3.6
24–35.9	26	0.6	0.2–1.5
36–59.9	35	0.4	0.1–1.3
60–120	37	0.4	0 1–1 0

c. Retinol binding protein/creatinine ratios

Age (months)	*No.*	*Mean (µg/mmol)*	*95% confidence limits (µg/mmol)*
0–2.9	16	46.4	3.8–570
3–11.9	11	5.9	3.2–11.0
12–23.9	16	12.0	2.0–70.2
24–35.9	21	8.2	3.1–22.1
36–59.9	33	7.5	3.0–19 2
60–120	36	6.8	2.4–19.4

d. Alanine aminopeptidase/creatinine ratios

Age (months)	*No.*	*Mean (IU/mmol)*	*95% confidence limits (IU/mmol)*
0–2.9	19	9.6	3.6–25.2
3–11.9	21	4.7	1.1–19.6
12–23 9	27	2.7	0.8–9.3
24–35.9	26	2.1	0.7–2.2
36–59.9	36	1.6	0.8–3.2
60–120	37	1.3	0.7–2.5

e. Alkaline phosphatase/creatinine ratios

Age (months)	*No.*	*Mean (IU/mmol)*	*95% confidence limits (IU/mmol)*
0–2.9	19	3.3	1.0–10.7
3–11.9	16	2.4	0.2–25.4
12–23.9	20	1.3	0.3–6.5
24–35.9	20	1.0	0.2–3.9
36–59.9	30	0.5	0.3–1.1
60–120	35	0.4	0.2–1.1

f. Gamma glutamyl transferase/creatinine ratios

Age (months)	*No.*	*Mean (IU/mmol)*	*95% confidence limits (IU/mmol)*
0–2.9	19	10.5	4.6–24.0
3–11.9	21	10.7	4.4–28.3
12–23.9	27	6.9	3.1–15.7
24–35.9	26	6.2	3.2–12.1
36–59.9	36	5.8	3.0–11.0
60–120	37	4.4	2.4–8.4

g. Lactate dehydrogenase/creatinine ratios

Age (months)	*No.*	*Mean (IU/mmol)*	*95% confidence limits (IU/mmol)*
0–2.9	19	11.4	1.6–79.3
3–11.9	20	6.6	1.2–35.4
12–23.9	26	2.6	0.3–21.0
24–35.9	26	2.0	0.5–7.4
36–59.9	36	1.4	0.3–7.4
60–120	37	1.2	0.4–4.3

h. N-acetyl-B-D-glucosaminidase/creatinine ratios

Age (months)	*No.*	*Mean (IU/mmol)*	*95% confidence limits (IU/mmol)*
0–2.9	19	1.65	0.59–4.12
3–11.9	21	0.87	0.49–2.81
12–23.9	27	0.46	0.18–1.14
24–35.9	27	0.36	0.14–0.92
36–59.9	36	0.28	0.13–0.62
60–120	37	0.25	0.13–0.50

by Werner *et al.* (1970) and for AAP by Jung *et al.* (1986). Bell *et al.* (1986) and Davies *et al.* (1984) found log distributions for albumin, whilst Gibb *et al.* (1989) found the same for RBP. A majority opinion supports a log normal distribution for urinary enzymes and proteins in early childhood.

The influence of sex was negligible. Differences have been reported for ALP, GGT, LDH and NAG by Maruhn *et al.* (1976), for LDH by Matsukura *et al.* (1987) and for GGT and NAG by Jung *et al.* (1986). Other studies found no difference, *e.g.* NAG by Price (1978), AAP by Jung *et al.* (1986) and ALP and GGT by Matsukura *et al.* (1987). The rapid fall in output of urinary proteins

Table 3 Summary of Analytes found to be Significantly Elevated in Patient versus Control Groups

Analyte	*Age (months)*	*Patient (mean)*	*Control (mean)*	*P*
Children with reflux				
NAG	36–120	0.32	0.27 IU/mmol	=0 03
LDH	36–120	2 0	1.3 IU/mmol	=0.015
GGT	12–35.9	8 3	6.6 IU/mmol	=0 018
Children with reflux and renal scarring				
Albumin	24–120	1.6	1.0 mg/mmol	=0.01
A_1M	36–120	0 63	0.38 mg/mmol	= <0.001
RBP	36–120	13.5	7.1 µg/mmol	= <0.001
AAP	36–59 9	2 1	1.6 IU/mmol	=0 018
NAG	36–120	0.33	0 27 IU/mmol	=0 016

seen in early life is probably the result of developing tubular maturity (Chantler, 1976) but later trends in enzymes and proteins may reflect differences in creatinine excretion and concentrating ability.

In this study we have shown that significant proteinuria in children with reflux is almost invariably associated with renal scarring. This is in agreement with the study by Bell *et al.* (1986), who measured albumin and RBP in such children and found higher levels in those with scars; however, many patients had normal levels of both analytes even when scarring was severe. White *et al.* (1987) also found a correlation between total proteinuria and the degree of renal scarring, but not the grade of reflux; these authors did combine age groups, which could not be done here owing to the marked age-related variations demonstrated.

Our results show that losses of albumin are increased in children with scarring, and this would accord with the glomerular damage seen on histological examination of advanced reflux nephropathy (Kincaid-Smith, 1975). It was unfortunate that such significant age-related changes were seen in all analytes because this meant that, because of inadequate numbers, comparison between results in children with different severity of scars could not be performed.

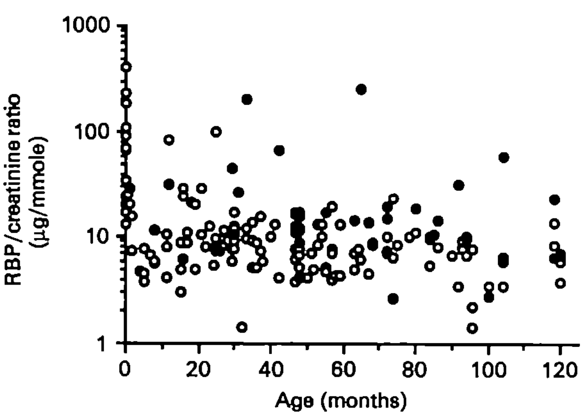

Fig. 2 Retinol binding protein/creatinine ratios in health (open circles) versus reflux with scarring (filled circles).

Gutteberg *et al.* (1987) noted a trend towards higher B_2M excretion from kidneys with reflux, some of which were scarred. We could not confirm this using alternative tubular proteins but we did not use their method of selective ureteric catheterisation.

Carvajal *et al.* (1975) used LDH to differentiate between upper and lower urinary tract infections, finding that infections involving the kidney were associated with a much higher urine enzyme activity. These findings were not confirmed by Hellerstein *et al.* (1988). It was interesting that LDH was one of the 3 enzymes (LDH, GGT and NAG) which was significantly raised in the older children with reflux whose urine was proved to be sterile. When high, this enzyme may suggest parenchymal injury not evident on renal imaging.

NAG is one of the simplest urinary enzymes to measure because of its stability when stored at −20°C without pre-treatment and the relative lack of assay interference. This dispenses with the need for storage pre-treatment and gel chromatography (Wellwood *et al.*, 1976). We found higher levels of this enzyme in the 36–120 month age group of children with reflux, with or without renal scarring. This trend has been previously described but there is still the problem of much overlap of results with the normal range. Kunin *et al.* (1978) found high levels of NAG in 5 of 9 children with reflux, although 2 of these had bacteriuria. Hultberg and Wieslander (1982) assayed urinary NAG in 50 children with reflux and found increased levels in those who had either a current urinary infection or renal impairment. Osborne (1980) estimated the normal range of NAG in children, but found normal levels in 6 with reflux.

The purpose of this study was to identify any urinary protein or enzyme which may be of value in the detection of children with sterile reflux. These children are at risk of developing renal scarring should urinary infection supervene. LDH, GGT and NAG enzyme activities were found to be increased in children with reflux in certain older age groups. The increase in tubular proteins A_1M and RBP was highly significant in many patients with reflux and renal scarring ($P < 0.001$), but for all analytes there was much overlap with controls.

There were, unfortunately, no markers amongst those chosen which showed potential for the early diagnosis of reflux before scarring has occurred. Most of the analytes measured are of proven value in the detection of renal parenchymal damage in such conditions as drug or heavy metal toxicity in animal models and industrial screening programmes. The implications must be that either sterile reflux is not itself causing damage to the renal tubules, or the markers used were not sufficiently sensitive to detect it. One of the complicating features of this study has been the wide variation of enzyme and protein levels seen in children of different age groups. If a promising substance was identified, a fuller assessment would have to be made of its normal range, particularly in the first few months of life when renal physiology is rapidly changing.

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Assessment of the Use of Bladder Washouts/ Instillations in Patients with Long-term Indwelling Catheters

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Summary—A randomised cross-over study of 3 bladder washout treatments—saline, Suby G and Solution R—was conducted on 25 elderly females with long-term catheters in order to examine crystal formation and catheter encrustation. With 2 exceptions, all patients produced crystals; only 14 completed the study. While a significant reduction in struvite crystals was found in the returned acidic washout fluid, there was no significant reduction of crystals in the neutral (saline) washout following any of the 3-week periods of treatment. Uric acid crystals appeared with Suby G and Solution R and these solutions were associated with higher red cell deposits in the urine. There was no significant difference in catheter encrustation between the various washouts.

Indwelling catheters are widely used in intractable urinary incontinence. Chronic bacteriuria is acknowledged to be an inevitable problem (Warren *et al.*, 1981) and catheter encrustation by struvite is known to be associated with the alkaline conditions caused by ammonia produced from urine by bacterial action (Griffith, 1978). Persistent infection with *Proteus mirabilis*, which raised urine pH to 6.8 or over, resulted in increased catheter encrustation (Hedelin *et al.*, 1991). Encrustation may occur on the tip and balloon of the catheter and may damage the urethral epithelium during catheter removal (Ekelund and Johansson, 1979; Lowthian, 1988). Catheter blockage by encrustation of the lumen can lead to catheter bypassing or to bladder overdistension causing trabeculation, bladder diverticula and detrusor myopathy (Hinman, 1970).

Bladder washouts and instillations are frequently used in attempts to prevent catheter encrustation, but the rationale for their use is still unclear. Daily irrigation with normal saline showed no significant effect on the incidence of total catheter replacements or obstructed or leaking catheters (Muncie *et al.*, 1989). Bladder irrigation may not only be ineffective but can cause a significant increase in urothelial cell exfoliation rates (Elliot *et al.*, 1989). Roe (1989) found nurses unclear as to the rationale for giving bladder washouts and felt that antiseptic washouts were being recommended too frequently.

The effectiveness of acidic washouts specifically designed to prevent or treat catheter encrustation has yet to be proved. An *in vitro* study by Hesse *et al.* (1989) using saline and citric acid showed that saline allowed the development of catheter encrustation, whereas a citric acid solution—Suby G—prevented this. Kennedy (1984) studied the effect of using Suby G and chlorhexidine alternately in a group of elderly catheterised patients and found encrustation was significantly reduced when compared with conventional saline bladder washouts.

The present study was undertaken to compare 2 acidic washout solutions, designed to dissolve encrustations, with neutral saline washouts in a group of elderly catheterised females. Approval for the study was given by the local Ethical Committee.

Patients and Methods

The patients were recruited from a population of elderly females in long-term care in the geriatric units of 3 hospitals. Six wards were visited and all long-term catheterised females were included. All patients had been catheterised before the start of the study.

The study comprised a within-patient comparison of 3 different solutions:

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Sodium chloride:	sodium chloride 0.9% (Solution A).
Suby G:	citric acid 3.23%, light magnesium oxide 0.38%, sodium bicarbonate 0.7%, disodium edetate 0.01% (Solution B).
Solution R:	citric acid 6%, gluconolactone 0.6%, light magnesium carbonate 2.8%, disodium edetate 0.01% (Solution C).

These solutions are available in 100 ml sterile pre-packed sachets called Uro-tainers and were provided by CliniMed. At the start of the trial they were all in current use at the hospitals.

The order in which the 3 solutions were given was determined by random number tables. The patients all received the 3 study solutions, but in different orders so as to minimise the influence of any time effects.

Week 1	Normal saline washout twice weekly (neutral period).
Weeks 2–4	Solution A, B or C twice weekly.
Week 5	Normal saline twice weekly (neutral period).
Weeks 6–8	Solution A, B or C twice weekly.
Week 9	Normal saline twice weekly (neutral period).
Weeks 10–12	Solution A, B or C twice weekly.

The catheter was changed at weeks 1, 5 and 9 and at the end of the trial—week 12. The catheters used were the type the patient was already wearing. At the time of each catheterisation a specimen of urine was obtained and sent for bacteriological analysis (4 per patient).

The washout fluid was instilled by allowing the sachet contents to flow through the catheter into the bladder by gravity; gentle pressure was sometimes required. The sachet tube was clamped and the solution was left in the bladder for a minimum of 20 min (maximum 30). The clamp was then released and the washout fluid specimen retained for examination. This specimen was spun and then examined microscopically, noting the presence of crystals, epithelium pus cells, urothelial cells and red blood cells.

The catheters were all collected and examined for encrustations. The degree of encrustation was noted using a visual analogue scale, recording encrustation at 3 sites: tip, balloon and lumen. A record was kept for each patient on the number of episodes of bypassing, any non-routine catheterisations, any antibiotics used and any problems arising from the catheter. These observations were kept by the ward nursing staff.

Statistical analysis

The outcome measures were analysed separately. A series of mathematical models was fitted to each measure using the method described by Aitken (1978). The 5 washout fluid measures (presence of crystals, urothelial cells, pus cells, red blood cells and bacteria) and the presence of a leaking washout were assumed to follow binomial distributions; the logistic transformation was applied and the probabilities of each outcome occurring computed for each treatment.

Catheter times *in situ*, the 3 encrustation measures and the number of bypassing episodes per week were considered to be continuous measures and to follow Normal (Gaussian) distributions. The distribution assumptions were tested by examining the residuals from the mathematical models and constructing probability plots (Draper and Smith, 1981); the extent to which the plots supported the hypothesis of an underlying binomial or Normal distribution was tested using the Filliben correlation coefficient (Filliben, 1975).

The mathematical models used evaluated the individual effects of washout fluid, time and treatment order as well as the interaction between washout fluid and time (*i.e.* significantly different changes over time for the 3 washout fluids). There were insufficient data to support an analysis of any possible interactions involving treatment order.

The significance of the factors assessed was determined by constructing standard analysis of variance and analysis of deviance tables for the continuous and dichotomous variables respectively. Significant differences in these tables were evaluated in detail using the Tukey multiple comparison test. The method of analysis used provided separate estimates of within-patient and between-patients variation; only the within-patient variance was used to test for differences between the 3 treatments.

The computations were performed using the GLIM 3.77 statistical computer program (Baker, 1985). Statistical significance was set at the conventional 5% level.

Results

Twenty-five patients were entered into the trial (mean age 82 years, range 65–100). They had been catheterised for a median of 12 months (range 1–204). Fourteen patients completed the full 12 weeks; 5 patients died (2 at week 11 and 3 earlier); 3 had their catheters removed; 2 were withdrawn from the trial at the request of nursing staff and 1 went home and was unavailable for follow-up. A total of 239 saline washouts, 127 treatments with Suby G and 111 treatments with Solution R were given.

Examination of washout fluid

Crystals

Crystals were observed in every patient at some time during the study, except for one in whom only yeasts were identified and one who died during the third week.

Four types of crystal were noted:

1. Struvite—magnesium ammonium phosphate. This was the most commonly seen crystal, observed in all but 5 patients. Struvite was identifiable as being trapezohedral or "coffin-shaped".
2. Calcium oxalate was observed in 4 patients in the octahedral or dihydrate form (two 4-sided pyramids stuck together).
3. Uric acid was observed in 10 patients in an interlocking colourful stellar formation and also as individual shards.
4. Sodium urate was observed in 4 patients as a small crystal looking like a conker in its shell.

In 5 cases crystals were observed but not identified.

Significantly more crystals were observed during saline washouts than during use of the acidic solutions (chi-squared (2) = 29.06, $P<0.001$) (Table 1). Different types of crystal were present in each washout fluid (Table 2). Struvite appeared significantly more often in the saline washouts and was rarely observed in Suby G and Solution R (chi-squared (2) = 22.075, $P<0.001$). The other crystal types were observed less often, but uric acid was identified mainly in Solution R and Suby G. Calcium oxalate was slightly more common in saline washouts than during the acidic treatments. Urates were seen only during saline washouts.

These differences are likely to be the immediate effect of the washout solution on the crystals contained in them. The long-term effect of the individual washout periods was assessed by exam-

Table 1 Observations of Washout Fluid (percentages of patients)

Treatment	*Treatment no.*	*Crystals (%)*	*Urothelia (%)*	*WBC (%)*	*RBC (%)*	*Bacteria (%)*
Saline	a	29	90	92	25	74
	b	50	92	92	9	84
	1	38	82	76	0	88
	2	39	100	96	8	92
	3	46	94	92	18	88
	4	34	94	100	17	96
	5	48	100	100	21	84
	6	40	100	100	21	100
Suby G	a	12	96	92	20	75
	b	34	96	96	11	85
	1	21	91	95	28	77
	2	20	100	96	31	93
	3	12	100	92	28	75
	4	22	100	99	27	84
	5	8	100	91	42	93
	6	17	86	87	17	75
Solution R	a	26	100	100	14	75
	b	43	96	100	14	92
	1	8	100	96	22	77
	2	8	96	84	22	79
	3	16	92	100	16	100
	4	8	96	100	4	89
	5	23	82	80	12	79
	6	23	100	84	14	76

a and b refer to neutral saline washout period.
1–6 refer to washout treatment—2 treatments per week
WBC—White blood cells.
RBC—Red blood cells.

Table 2 Type and Frequency of Crystals Observed in Washout Fluid

	Saline	*Suby G*	*Solution R*
Total no of washouts	239	127	111
Crystal type			
Struvite	69	7	2
Uric acid	1	6	9
Calcium oxalate	21	11	5
Urates	4	0	0
Unidentified	3	0	2
Yeasts	0	4	0

ining for the presence of crystals during the neutral weeks (weeks 5 and 9) relative to the washout used in the preceding 3 weeks (Table 3). No significant difference was found in the presence of crystals between the 3 treatments during this neutral period, although in all cases there was an increase in the occurrence of crystals when compared with observations made during week 1 of the study.

Catheter encrustation

The effect of the washout on catheter encrustation was studied by examination of catheters following use. In all, 120 catheters were inserted during the study and 100 were examined for encrustation (20 were not saved). Blocked catheters were defined as having the eyes or the lumen completely blocked, resulting in no flow of urine. Catheters which were partially blocked were still able to allow urine drainage. Overall, Solution R produced the best results and Suby G gave the worst (Table 4). However as might be expected, a time effect was noted (Table 5), since blocked catheters tended to be removed earlier and those lasting for longer periods *in situ* were not blocked. There was little difference between the 3 treatments up to day 10, after which Solution R did not reduce encrustation as well as Suby G or saline.

Urothelial cells

These were found to be present in most samples (Table 1). They were observed singly and commonly in clumps containing several cells. There was some evidence of a significant difference in the changes over time within the 3 treatments (chi-squared (14) = 22.5, $P = 0.068$) but the proportions were all consistently high, so it is unlikely that the differences were clinically significant.

White blood cells

White blood cells were present in a high percentage of samples (Table 1). No significant differences arose between the 3 treatments.

Red blood cells

Red blood cells were seen occasionally in all but 3 patients (Table 1). There were significant differences between the treatments (chi-squared (2) = 7.18, $P = 0.028$) and these were consistent over the treatment period; the cause of the difference was the notably higher red blood cell count in the Suby G period relative to the other 2 treatment periods. One patient developed frank haematuria following treatment with Solution R. This stopped when Suby G was administered.

Bacteria

Bacteria were observed at some point in every patient and were present in a high percentage of samples (Table 1). Suby G and Solution R appeared to reduce the level of bacteria, but the results were extremely variable and failed to reach statistical significance. Of 66 specimens of urine that were analysed for the 25 patients, 4 showed no significant growth of bacteria; 3 of these followed antibiotic therapy and the fourth followed saline washouts. At the end of each treatment period, therefore, there was no elimination of bacteria. Eighteen specimens (27%) showed the presence of known urease-producers (*Proteus mirabilis, Pseudomonas* and *Providencia stuartii*). Analysis of the data showed no significant association between the type of bacteria and the presence of crystals in this relatively small number of patients. Urease-producers were found in 21% of specimens following saline treatment, 56% following Suby G and 21% following

Table 3 Crystal Frequency during Neutral Periods

	At onset Week 1	*Following saline*	*Following Suby G*	*Following Solution R*
Total no. of washouts	50	24	27	26
% no crystals	70	62.5	59.3	53.9
% with crystals	30	37.5	40.7	46.1

Table 4 Examination of Catheters

Treatment	*Total*	*Not encrusted (%)*	*Partially blocked (%)*	*Blocked (%)*
Saline	44	12 (27)	14 (32)	18 (41)
Suby G	29	3 (10)	12 (42)	14 (48)
Solution R	27	10 (37)	10 (37)	7 (26)

Solution R. Thus treatment with acidic solutions did not prevent or even reduce urease-producers.

Time in situ

Each catheter remained *in situ* for the full 28 days of each treatment period in only 3 patients. The mean time *in situ* was 16.3 days (saline), 14.3 days (Suby G) and 14.2 days (Solution R). No significant differences were found.

Catheter bypassing

The mean number of episodes of bypassing per week was 1.55 (saline), 1.4 (Suby G) and 1.9 (Solution R). The differences were not statistically significant.

Discussion

Bladder washouts and instillations have been advocated as means of preventing and treating catheter-associated infections. Although this study was not designed to reduce catheter-related infection, the results showed that treatment with Suby G and Solution R did not eliminate bacteria or have any effect on bacteria producing urease.

Crystal formation, particularly struvite, was found to be virtually universal. Although all patients produced crystals, not all went on to have blocked catheters. The types of crystal observed during this study have also been noted in previous work. Struvite has been most commonly associated with catheter encrustations, as noted by Hukins *et al.* (1983). Calcium oxalate, uric acid and urates have also been observed in the encrustations analysed from catheters (Hedelin *et al.*, 1984).

Calcium oxalate was observed in the dihydrate form. Calcium oxalate crystals can be observed in normal subjects and may be due to insufficient fluid intake or excessive secretion of calcium, phosphate or oxalate (Rose, 1982). Uric acid crystals have been associated with pH below 6.0, reduced urine volumes and chronic dehydration (Seftel and Resnick, 1990). Urates are associated with alkaline urine (Smith, 1978).

It was expected that acidic washouts would reduce encrustations due to struvite. There was certainly a significant reduction in crystals present in washout fluids containing Suby G and Solution R but not saline, but there was no difference between the 3 regimes at the end of each 3-week period. It can, therefore, be concluded that twice-weekly acidic washouts did not diminish crystal formation.

Catheter encrustation was shown to relate mainly to the length of time the catheter was *in situ* (virtually a tautology). While Solution R produced a higher percentage of catheters free from encrustation, it showed much higher mean scores for encrustation in catheters remaining *in situ* longer

Table 5 Catheter Encrustation: Change over Time

Area of catheter	*Treatment*	*Mean Score over time in situ (days)*						
		0–2	*3–6*	*7–9*	*10–13*	*14–20*	*21–27*	*28*
Tip	Saline	2.9	2.6	2.2	1.9	1.5	0.8	0.08
	Suby G	3.3	3.0	2.5	2.1	1.7	0.9	0.03
	Solution R	3.0	2.9	2.8	2.7	2.6	2.4	2.2
Balloon	Saline	2.0	1.8	1.6	1.4	1.2	0.8	0.4
	Suby G	2.4	2.2	1.9	1.7	1.4	0.9	0.4
	Solution R	2.6	2.5	2.3	2.2	2.1	1.8	1.6
Lumen	Saline	4.4	3.9	3.4	3.0	2.4	1.4	0.4
	Suby G	5.5	4.9	4.1	3.5	2.8	1.4	0.05
	Solution R	4.7	4.4	4.0	3.7	3.3	2.7	2.0

Visual analogue scale

0 ______________________________ 10 tip

0 ______________________________ 10 balloon

0 ______________________________ 10 lumen

0 = No deposits. 10 = Completely covered.

than 3 days. These findings are somewhat contradictory.

Uric acid crystals were strongly identified with acidic washouts. Presumably these allowed uric acid to precipitate out of the urine. Seven blocked catheters occurred during treatment with Solution R. Three of these could have been due to encrustation with uric acid crystals which had been identified in washouts given immediately prior to the catheters becoming blocked. It may be that acidic washouts are contraindicated in patients with dehydration and/or a low urine output—conditions which have been associated with formation of uric acid calculi (Seftel and Resnick, 1990). This needs further investigation.

It seems that some patients are blockers and others non-blockers of catheters (Kunin *et al.*, 1987a and b). Catheter replacements follow patient-specific patterns; certain patients always have catheters removed due to obstruction (Muncie and Warren, 1990). This study found 3 patients who never produced encrusted catheters, although they did produce some crystals. The majority of the patients in the study, however, must be considered potential blockers.

All patients produced high levels of urothelial cells, which concurs with the findings of Elliot *et al.* (1989), *i.e.* irrigations lead to an increased shedding of urothelial cells. However, in this study no baseline measurement was made of urine samples taken before washout therapy. White blood cells and bacteria were found at high levels throughout. Red blood cells were higher during Suby G treatment, indicating possible irritation to the bladder mucosa. Another indication of bladder irritability during Suby G treatments was the increased probability of leaking washouts.

The study has shown that long-term catheterised patients tend to be crystal formers. Acidic washouts administered twice a week for 3 weeks did not have a demonstrable effect in preventing crystal formation or catheter encrustation and the frequency of red cells in the urine with these washouts suggests an adverse effect on the bladder endothelium. Further work on the frequency of administration of washouts is needed.

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Morphological Effects of Photodynamic Therapy on Rabbit Bladder Using Photofrin II and Photosan Intravesically and Intravenously

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Summary—Photodynamic therapy (PDT) has proved effective against superficial papillary bladder tumours and focal and diffuse carcinoma *in situ*. Effective topical administration of the sensitiser would be a welcome improvement.

The morphological effects of PDT on the normal bladder were examined in 13 rabbits when 2 photosensitisers (Photofrin II and Photosan III) were applied intravesically (5 mg/kg for 1 h) and compared with intravenous administration (3 or 5 mg/kg). Four animals served as controls without a sensitiser. Intravesical red light (630 nm) from an argon dye laser was used to activate the photosensitiser, using light doses of 12 or 24 J/cm^2. The animals were sacrified either 1 or 5 to 7 days after the laser treatment.

Intravenous dosage induced bladder wall oedema/haemorrhage and total necrosis of the epithelium. There was no difference between the effects of the 2 sensitisers. Intravesical application induced superficial epithelial necrosis. The control animals treated with laser light alone showed slight superficial injury to the cell layer.

Photodynamic therapy (PDT) is an experimental form of cancer treatment based upon the use of a photosensitising agent, the presence of oxygen, and exposure to non-ionising radiation. This combination can result in significant cytotoxicity (Benson, 1989). PDT involves the systemic administration of a sensitising drug which is retained in neoplastic tissue with a small degree of selectivity (Pope and Bown, 1991). After an interval, the tumour is illuminated with laser light at a wavelength which activates the photosensitiser. The light energy is taken up by the sensitiser and, by means of a photochemical reaction in the presence of oxygen, cell destruction occurs (Plail *et al.*, 1990).

Kelly and Snell (1976) were the first to use PDT in the treatment of bladder cancer. It proved effective against superficial papillary bladder tumours as well as focal and diffuse carcinoma *in situ* (Prout *et al.*, 1987; Benson, 1989; Harty *et al.*, 1989).

The optimum therapeutic parameters are not yet known. Most investigators have used haematoporphyrin derivative (HpD) and dihaematoporphyrin ether or ester (DHE) as a sensitiser, but the lack of specificity can lead to photosensitivity in other organs. The most common adverse effect of PDT is cutaneous photosensitivity, depending on the photosensitiser used. Some authors have reported bladder muscle fibrosis and permanently reduced bladder capacity, incontinence and upper tract deterioration (Harty *et al.*, 1989). Effective topical application of the sensitiser would be a welcome improvement (Benson, 1989).

The aim of the present study was to investigate the morphological effects of PDT on the normal bladder when 2 photosensitisers were applied intravesically and compared with intravenous administration.

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Materials and Methods

Eighteen adult male rabbits weighing 1.9–4.0 kg (mean 2.7) were used. The animals were anaesthetised with intramuscular ketamine hydrochloride (Ketalar 50 mg/ml) 50 mg/kg. An ear vein was cannulated and anaesthesia maintained with intravenous ketamine hydrochloride or pentobarbital sodium (Mebunat).

The photosensitisers were dihaematoporphyrin ether (Photofrin II) 2.5 mg/ml (QLT Phototherapeutics Inc., Lederle, Pearl River, New York, USA) and haematoporphyrin derivative (Photosan III) 3.3 mg/ml (Dr R. Koch GmbH, Vienna, Austria).

Seven rabbits received an intravenous injection of the photosensitiser (Photofrin II 5 mg/kg, 2 rabbits; Photosan III 3 mg/kg, 5 rabbits). Six rabbits were catheterised with 12F Teflon coated Foley catheters and the bladders were emptied. The photosensitisers were administered intravesically (Photofrin II 5 mg/kg, 2 rabbits; Photosan III 5 mg/kg, 4 rabbits) for 1 h. The bladder was then emptied and the catheter removed. Four animals served as controls without a sensitiser; they received only the photoradiation therapy. One animal served as a control without a sensitiser or the photoradiation.

After an interval of 24–48 h the animals were anaesthetised again and a midline laparotomy was performed. The bladders were catheterised and filled with saline, and the laser fibre was introduced into the bladder through a cystotomy.

An argon (Lasermatic PDT 630, Lasermatic Inc., Helsinki, Finland) pumped Kiton Red laser (wavelength 630 nm) was used. The light passed down a 320 μm fibre with a 0.5 mm diameter spherical ball tip. The power output and wavelength were examined before commencing treatment. The energy densities were 12 J/cm^2 (340 mW 30 min) or 24 J/cm^2 (500 mW 40 min).

After treatment, the cystotomy and laparotomy wounds were closed with absorbable sutures and the bladders were emptied. The animals were sacrificed either 1 or 5 to 7 days later and the bladders were dissected. The changes were analysed macroscopically and specimens were taken for analysis by light microscope and scanning electron microscope (SEM).

Table Results of PDT on the Rabbit Bladder with Intravenous and Intravesical Administration of the Sensitiser

		Bladder wall changes				
		Macroscopic changes	*Light microscope*		*SEM*	
	Days		*Inflammation*	*Epithelial injury*	*Inflammation*	*Epithelial injury*
Intravenous						
Photofrin 12 J/cm^2	1	+++	+++	+++	++	++
24 J/cm^2	1	++	+++	+++	++	+++
Photosan 12 J/cm^2	1	+++	+	+++	+	++
	5	+++	++	++	–	+
	7	+++	+++	+++	–	+
24 Jcm^2	1	+++	–	+	–	++
	5	+++	++	++	–	++
Intravesical						
Photofrin 12 J/cm^2	1	+	–	+	–	+
24 J/cm^2	1	+	–	–	–	+
Photosan 12 J/cm^2	1	+	+	–	–	+
	6	+	–	–	–	++
24 J/cm^2	1	++	–	–	–	++
	6	++	–	–	–	++
Control (no sensitiser)						
12 J/cm^2	1	–	–	+	–	+
	5	–	–	–	–	±
24 J/cm^2	1	–	–	+	–	±
	5	–	–	–	–	++

– = no change, ±, +, ++, +++ = marked changes.

Multiple specimens from each animal for light microscope analysis were fixed in phosphate buffered (pH 7.0) 4% formaldehyde solution, embedded in paraffin, sectioned and stained with haematoxylin and eosin. The findings were scored according to epithelial injury and bladder wall reaction (inflammation, oedema, haemorrhage).

The specimens for SEM analysis were washed with 0.1 M phosphate buffer (pH 7.4) before fixation in 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for 12 h. The specimens were dehydrated in ethanol and dried in a Balzers Union CPD 020 Critical Point Dryer according to the recommendations of Andersson (1951). The specimens were coated with 200 Å thick gold in a Jeol Fine Coat Ion Sputter JFC-1100 (1.2 kV, 5–10 mA, 6 min) and viewed in a Jeol JSM-820 SEM (7–12 kV acceleration). The views were photographed and analysed. The findings were assigned to 5 categories according to epithelial injury and superficial inflammatory changes (− = no change, ±, +, ++, +++ = marked changes).

Results

The results are summarised in the Table.

Macroscopically, bladder wall oedema and haemorrhages were seen following intravenous administration of both sensitisers. No difference was seen macroscopically between the effects of the 2 sensitisers or the light doses (12 or 24 J/cm^2) when intravenous administration was used. After intravesical application the macroscopic changes were minimal.

Light microscope analysis showed that the light energy alone did not cause any changes in the bladder wall (Fig. 1). In some animals PDT with intravesical administration induced mild bladder wall oedema (Fig. 2). The marked changes after intravenous administration of both light sensitisers were almost equal (Fig. 3).

On SEM analysis the light energy alone induced a superficial cell layer injury possibly due to a local heating reaction (Fig. 4) when compared with normal epithelium without radiation (Fig. 5). Intravesical administration caused increased superficial epithelial destruction (Fig. 6). Intravenous administration induced deep epithelial destruction with most of the epithelium being totally removed (Fig. 7). In these specimens inflammatory deposits were frequently seen.

The change in temperature in the bladder wall during PDT was approximately 3°C (measured in 3 animals). The affected cells started to desquamate during the experimental period of 7 days when the effect of therapy was superficial.

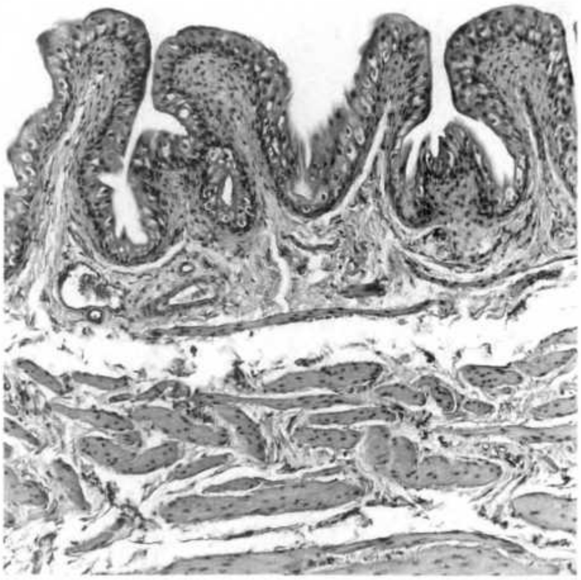

Fig. 1 Bladder wall after bare light irradiation. There are no epithelial, subepithelial or muscular layer changes. (H and E × 100).

Discussion

There are few reports on the intravesical application of a photosensitiser and the initial results are controversial.

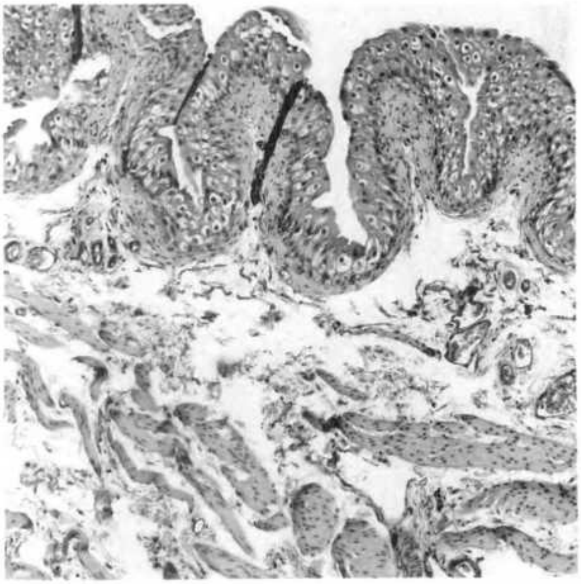

Fig. 2 Intravesical dosage of photosensitisers induced mild subepithelial and muscular layer oedema. (H and E × 95).

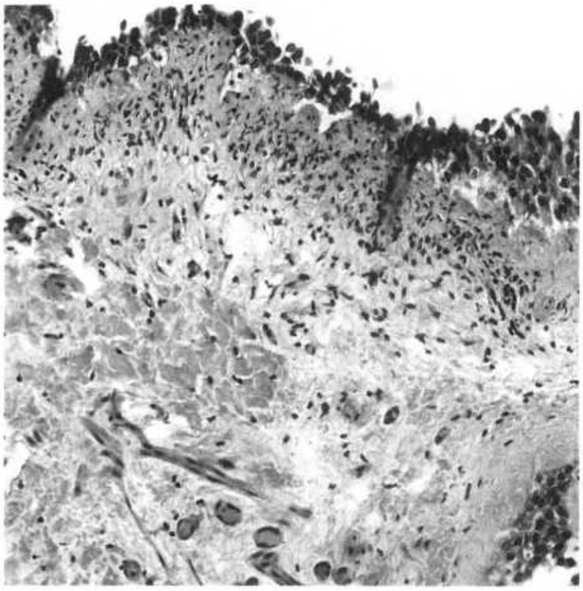

Fig. 3 Intravenous dosage of photosensitisers induced prominent changes in the bladder wall. Destruction of the epithelium is almost complete. There is a marked subepthelial inflammatory cell reaction. Large haemorrhages and oedema together with muscular destruction are seen in deeper layers. (H and E × 250).

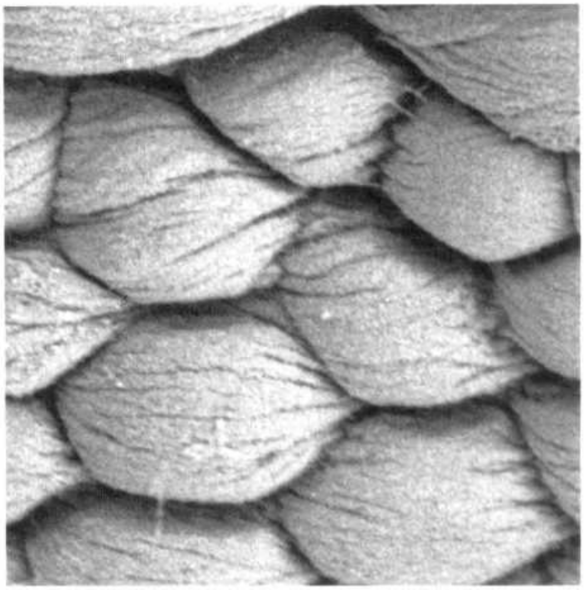

Fig. 4 Bladder epithelium on the first day after bare light irradiation. Superficial layer cells are wrinkled and many cell junctions are opened. (SEM × 800).

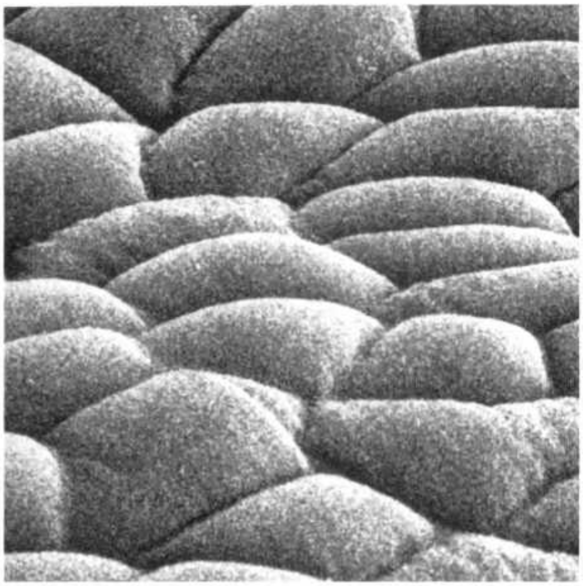

Fig. 5 Bladder epithelium of a control animal. Cells are smooth and junctions are tight. (SEM × 1000).

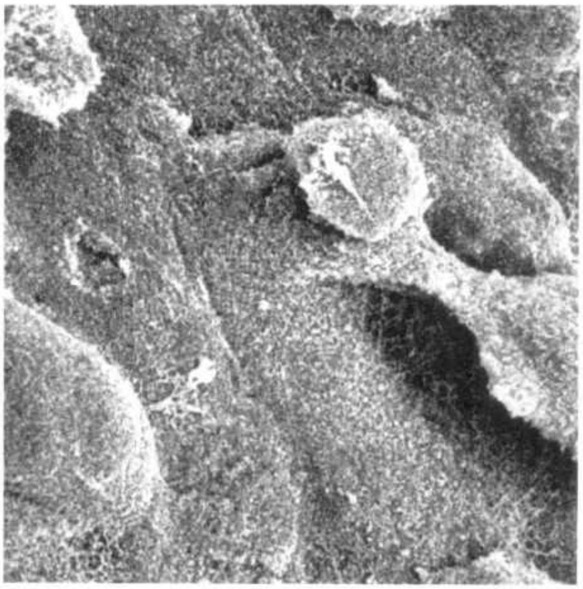

Fig. 6 Intravesical dosage induced superficial necrosis of epithelial cells (left). Most of the epithelium is covered with fibrin deposits. (SEM × 800).

Lin *et al.* (1984) examined the distribution of HpD fluorescence in 14 patients with transitional cell carcinoma of the bladder scheduled for cystectomy. They used intravesical instillation of HpD with dosages of 20 to 120 mg per patient (0.3–2 mg/kg), with the instillation time and volume of HpD being held constant at 90 min and 50 ml respectively. It was found that the overall distribution of

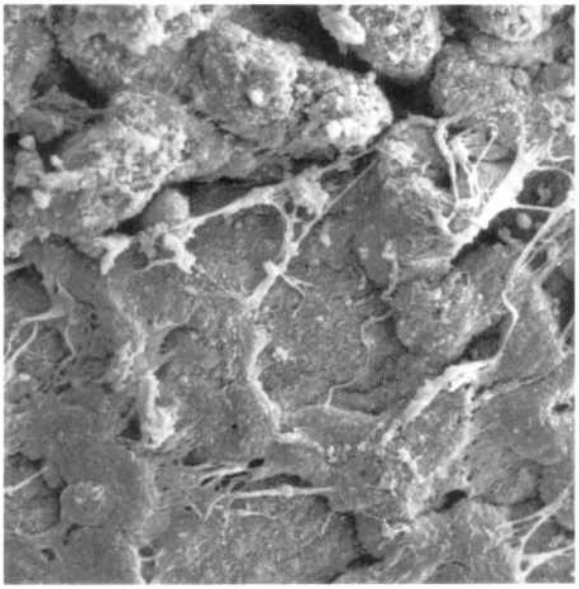

Fig. 7 Intravenous dosage induced marked destruction of the epithelium. Ghost of epithelial cells above and bare basement membrane below. (SEM × 500).

fluorescence did not correspond to the presence of a tumour and the highest intensity of fluorescence was often seen in areas of cellular degeneration, oedema and necrotic tissue. The authors concluded that intravesical instillation was not a useful means of administering HpD because of the lack of specificity of HpD localisation in tumour tissues and also because a significant percentage of tumour tissue did not take up HpD. It seems that the dosage they used (0.3–2 mg/kg) was too low.

Rosenberg and Williams (1986) and Benson (1989) investigated the topical application of HpD solutions in the bladder and reported moderate success, but they did not report the precise protocols and results.

Windahl *et al.* (unpublished data) studied the organ distribution of ^{14}C-labelled HpD in rats after intravesical and intravenous administration of the sensitiser. They found that the uptake of HpD in the bladder wall was about 100 times higher after intravesical instillation than after intravenous injection. The systemic absorption of HpD after intravesical installation was very low. We have had similar results with ^{125}I-labelled dihaematoporphyrin ether in rats. These observations suggest that intravesical administration of the sensitiser would be useful in bladder PDT.

Pope and Bown (1991) investigated the intravesical absorption of a new photosensitiser, aluminium sulphonated phthalocyanine (AlSPc) in the rat bladder, and found that direct absorption seemed unreliable. PDT following intravesical administration of AlSPc produced patchy and unpredictable results, often with areas of full thickness damage to those of minimal change. In the present study the damage to the superficial layers of the bladder wall was quite even.

The present results indicate that intravesical application of a haematoporphyrin derivative in PDT has only a slight effect on the normal bladder wall. Macroscopically, or following light microscope examination, only moderate differences were seen between the intravesical application group and the control group. SEM examination revealed marked epithelial changes when the sensitisers were applied intravesically, but light microscopy seems to be more suitable in determining the depth of PDT injury.

It is clear that the intravesical dose of the sensitisers used in the present study (5 mg/kg) was not sufficient to achieve epithelial necrosis in the bladder wall. Intravenous application, however, resulted in marked macroscopic and microscopic changes throughout the bladder wall. In order to minimise unwanted effects it seems necessary to limit the initial PDT damage to the superficial layers of the bladder wall (Pope and Bown, 1991). In clinical practice the recommended sensitiser dose with Photofrin II is 2 mg/kg (Prout *et al.*, 1987; Benson, 1989; Harty *et al.*, 1989). It seems that the intravenous dosage used (Photofrin II 5 mg/kg, Photosan 3 mg/kg) was too high for PDT in the bladder.

In clinical practice the recommended total light dose is 15–20 J/cm^2 for whole bladder illumination without focal treatment (Benson, 1988). Harty *et al.* (1990) used whole bladder radiation of 25 J/cm^2 and they also used focal illumination of 100 J/cm^2 for up to 4 papillary tumours per patient. They reported severe detrusor toxicity with these light doses. Detrusor toxicity seems to result from PDT damage to the deeper muscle, which does not regenerate as completely as urothelium and which heals with at least some fibrosis (Pope and Bown, 1991). In the present study there were no differences between the 2 light doses used (12 and 24 J/cm^2). There was a slight thermal effect on the epithelium which was evident in the SEM analysis. It seems that the suitable total dose is 15 J/cm^2 in whole bladder illumination.

It was concluded that the intravesical dose used in the present study was not sufficient to achieve deep epithelial necrosis of the bladder wall. Further studies with different dosages, new photosensitisers, and also combinations with penetrating drugs in a bladder tumour model, appear necessary.

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The Value of Nuclear Area as a Prognostic Factor in T1 Papillary Transitional Cell Carcinoma of the Bladder

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Summary—In a series of 131 T1 papillary transitional cell carcinomas of the bladder, the nuclear areas of 100 nuclei (50 from the external papillary zone and 50 from the internal papillary zone) were measured. An attempt was made to correlate retrospectively the value of the mean nuclear area with histological grade and with survival. A higher value was obtained for the mean nuclear area of the internal papillary zone than for that of the external papillary zone. A better survival rate was found after 10 years' follow-up for those tumours whose mean nuclear area in the internal papillary zone was $\leqslant 28\ \mu m^2$, which suggests that it is in this zone that the nuclear area should be measured. A correlation was observed between the increase in the mean nuclear area value and higher histological grade.

The most useful prognostic factors in superficial transitional cell carcinoma include tumour size, multifocality, presence of carcinoma *in situ*, mitotic index and histological grade. One of the main disadvantages of using these prognostic factors is the subjectivity involved in establishing most of them (Takashi *et al.*, 1987; Abel, 1988).

The prognosis of this kind of tumour has also been correlated with tumour markers, the most significant being surface antigens ABO(H), T antigen, chromosome abnormalities and DNA evaluation by flow cytometry (Javadpour *et al.*, 1982). Expensive and often sophisticated technology is also required to determine some of the tumour markers (*e.g.* DNA flow cytometry).

The importance of using morphometry to study tumour cells is that it is an objective and reproducible technique. It entails measuring a pre-selected set of tumour cell parameters.

In transitional cell carcinoma of the bladder, the parameter which seems to correlate best with histological grade is nuclear area (Helander *et al.*, 1985; Collan *et al.*, 1987a and b; Pesce, 1987).

The aim of the present study was to correlate retrospectively the nuclear area in a series of superficial transitional cell carcinomas of the bladder with survival, and thereby to find out if the nuclear area value could account for different prognoses for the tumour within the same category (T1).

Patients and Methods

From January 1973 to December 1983, 734 bladder tumour samples taken from 547 patients were studied by the Pathology Department.

A rigorous selection was made of these samples based on their quality and knowledge of the patients' evolution over at least 5 years (or date of death); 131 T1 papillary transitional cell carcinomas of the bladder were finally included in the study. All had been treated by transurethral resection. Patients who had also been treated with endovesical chemotherapy did not show increased survival.

The prognosis of the patients was considered to be survival expressed in years from the moment the bladder tumour was diagnosed.

The samples had been fixed for 24 to 48 h in 4% neutral buffered formalin, embedded in paraffin, sectioned at 4 to 6 μm and stained with haema-

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toxylin and eosin. Tumours were graded according to the classification of Bergkvist *et al.* (1965).

The nuclear area measurements were made using a semi-automatic MOP-VIDEOPLAN image analyser (Kontron, Germany), which consists of a central computer, an image processor and interactive system, together with an OLYMPUS BH2 light microscope and a camera lucida.

At a magnification of 1000 ×, a cursor was used to measure 100 nuclei for each tumour following the recommendations of Ooms *et al.* (1983) and Wehner (1986). In other words, 50 nuclei from the external papillary zone and 50 from the internal papillary zone were measured. (In this study the external and internal zones always refer to papillary zones). Care was taken not to measure more peripheral nuclei because, as Helander *et al.* (1985) pointed out, these are cell nuclei showing little activity which are on the point of flaking off and are, therefore, small in size.

To evaluate the accuracy of the measurements the coefficient of variation (CV) was applied as described by Collan *et al.* (1986) and Fleege *et al.* (1988). The value we obtained was 1.74, which is close to 1.5, the number around which the CV must lie to ensure the reliability of the method.

The statistical analysis was performed with the SIGMA program (Horus Hardware S.A., Madrid, Spain) in a BULL-MICRAL 30 computer.

Table 1 Comparison of Mean Nuclear Area (external and internal zone) in Superficial Carcinoma of the Bladder

Papillary carcinoma	*Mean nuclear area*	*SD*	*No. of patients*
External zone	29.4795	8 7808	131
Internal zone	32.1288	11 1695	131
Differences	−2.6492	7.6848	131

Statistical error = 0.67143; $t = -3.9457$; $P < 0.001$ significant

Results

Table 1 gives the measurements of the 50 nuclei in the external zone and the 50 in the internal zone.

To check if it made no difference which zone, external or internal, was used to measure the nuclei, or if, on the other hand, there were differences between the zones, a comparison was made between the means of the nuclear areas using a matching procedure (we considered that both external and internal measurements were effected on the same tumours). The result showed that the difference between the 2 zones was statistically significant ($P < 0.001$) (Table 1).

The 131 papillary tumours were reviewed to see if the mean nuclear area of any of the internal zone tumours was much larger than the mean nuclear area of the external zone and might, therefore, have produced the difference between the values for the 2 zones.

Four cases were found in which the internal zone value was larger than the external zone value by at least 20 μm^2. They were temporarily removed from the study while a further comparison of the means of the nuclear areas was made: again the internal zone had a higher mean nuclear area value than the external zone, and once again the difference was statistically significant ($P < 0.001$). This proved that the difference found in the earlier comparison had not been caused by these 4 cases, which were reintroduced into the study for later statistical calculations.

A comparison was made between the mean nuclear area of the external and internal zones, differentiating histological grade (Table 2). In the 22 Grade I cases, no differences were found between the 2 zones. There were, however, significant differences for Grades II and III, with the mean nuclear area of the internal zone being larger in both cases.

The mean nuclear area of the 100 nuclei measured (sum of the 50 nuclei corresponding to the internal

Table 2 Comparison of Mean Nuclear Area (external and internal zone) in Superficial Papillary Carcinoma according to Histological Grade

Histological grade	*External zone*	*Internal zone*	*SD*	*No of patients*	*Statistical error*	*Student's t test*	*P*
I	26.9534 ±9.5921	26 8321 ±8.8946	8.058	22	1 718	0.070612	NS
II	28 6979 ±7.1924	31.9808 ±10.8636	7.8058	89	0.82742	−3.9676	<0.001
III	35.7366 ±11.6035	38.6136 ±11.9459	6.267	20	0.9014	−2.953	<0.05

Table 3 Comparative Multiple-mean Test or Mean Nuclear Area in Superficial Papillary Carcinoma according to Histological Grade

Histological grade	*Mean nuclear area*	*SD*	*Statistical error*	*No of patients*
I	26.8928	8 3304	1.7761	22
II	30.3392	8.3453	0 8846	89
III	37.1751	11.3514	2.5382	20
Variable 1	*Variable 2*	*Difference*	*Fisher's f*	*P*
I	II	−3 4464	1.3364	<0.01
I	III	−10.2823	7.0646	<0 01
II	III	−6.8359	4.8672	<0.01

zone and the 50 to the external zone) was 30.841 $\mu m^2 \pm 9.2825$ (131 cases). By means of a comparative multiple-mean test, the mean nuclear areas of the papillary carcinomas were compared according to histological grade: the comparison showed that the higher the histological grade, the larger the nuclear area, and the differences between them were statistically significant (Table 3).

To check whether knowledge of the mean nuclear area of the 100 nuclei measured could account for different prognoses with category T1, a number of actuarial tables were made with different nuclear area values. We did not find a different prognosis when these values were above or below a given level. Figure 1 shows the actuarial table for a nuclear area $\leqslant 30$ or $>30\ \mu m^2$: survival is practically the same in both cases.

Since the mean nuclear area of the internal zone yielded the higher value, actuarial tables were made for this parameter. Significant differences were

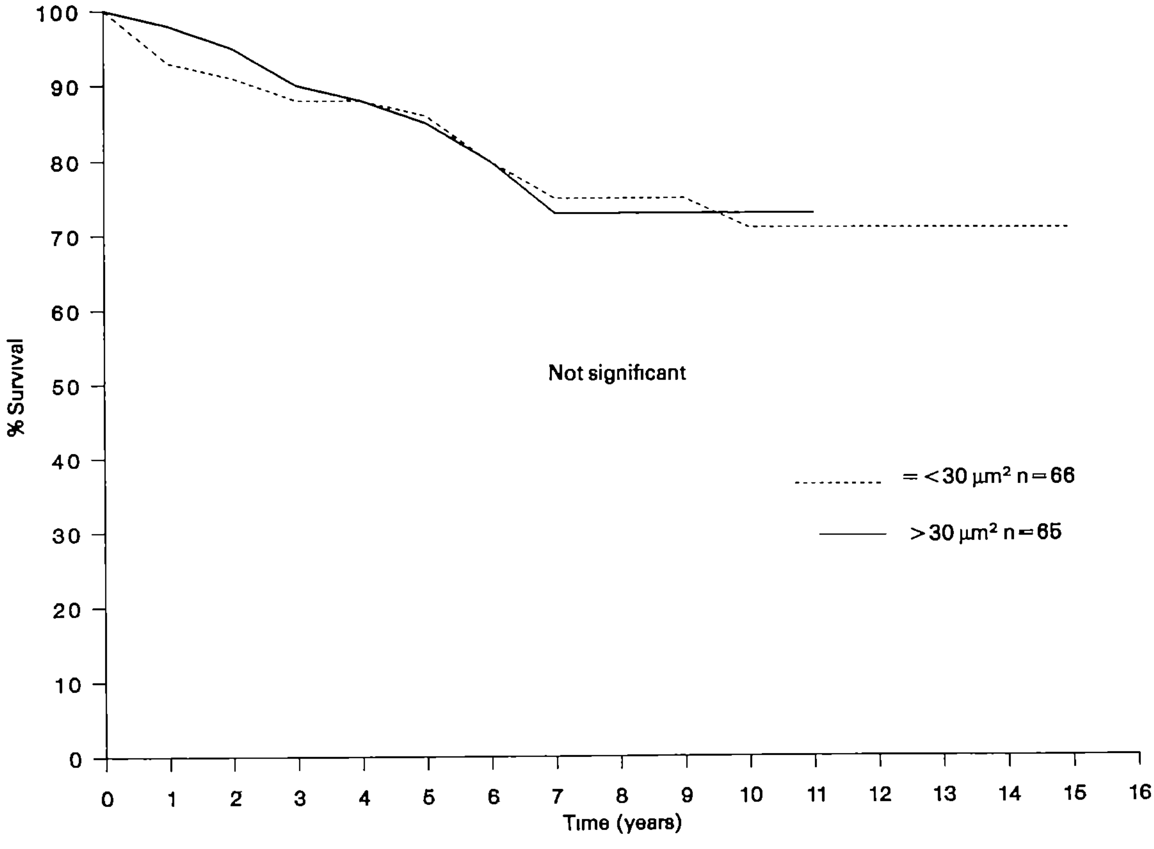

Fig. 1 Survival table for superficial papillary carcinoma in relation to nuclear area $\leqslant$ or $>30\ \mu m^2$.

found in survival after 10 years' follow-up for those tumours whose mean nuclear area measured $\leqslant 28$ or $>28\ \mu m^2$ (Fig. 2).

Figure 3 shows the different prognosis of the superficial papillary carcinomas according to their histological grade.

Discussion

Carcinoma of the bladder is one of the commonest tumours in man and displays high morbidity and mortality. In the United States it is the seventh highest cause of death in men and the ninth in women, with 40,000 new cases reported each year with an annual mortality of 11,000 (Thompson *et al.*, 1987). Although superficial carcinomas of the bladder have a better prognosis than invasive carcinomas, they show high morbidity because of their tendency to recur (as high as 70% for those treated only by transurethral resection) and to progress from low grade to high grade carcinomas (10–20%).

Until now the prognostic factors applied to superficial carcinoma of the bladder have not been reliable enough to establish with a degree of certainty which patients will suffer from progression and recurrence and will, therefore, require more aggressive treatment.

In the search to discover a parameter which might help to determine better the aggressiveness of the tumour, the morphometric study of the tumour cell was devised.

Knowing the mean nuclear area of the tumour cell can help to classify neoplasias objectively on the basis of numerical data, which are, therefore, reproducible. Montironi *et al.* (1986), Chan *et al.* (1987) and Van der Poel *et al.* (1988) reported their attempts to assign a histological grade to each tumour based on nuclear area values. Other authors, such as Lipponen *et al.* (1990), believe that 2 kinds of Grade II tumours can be differentiated through knowledge of their nuclear area, each having a different prognosis. Blomjous *et al.* (1990) also distinguished 2 types of tumour for Grade II

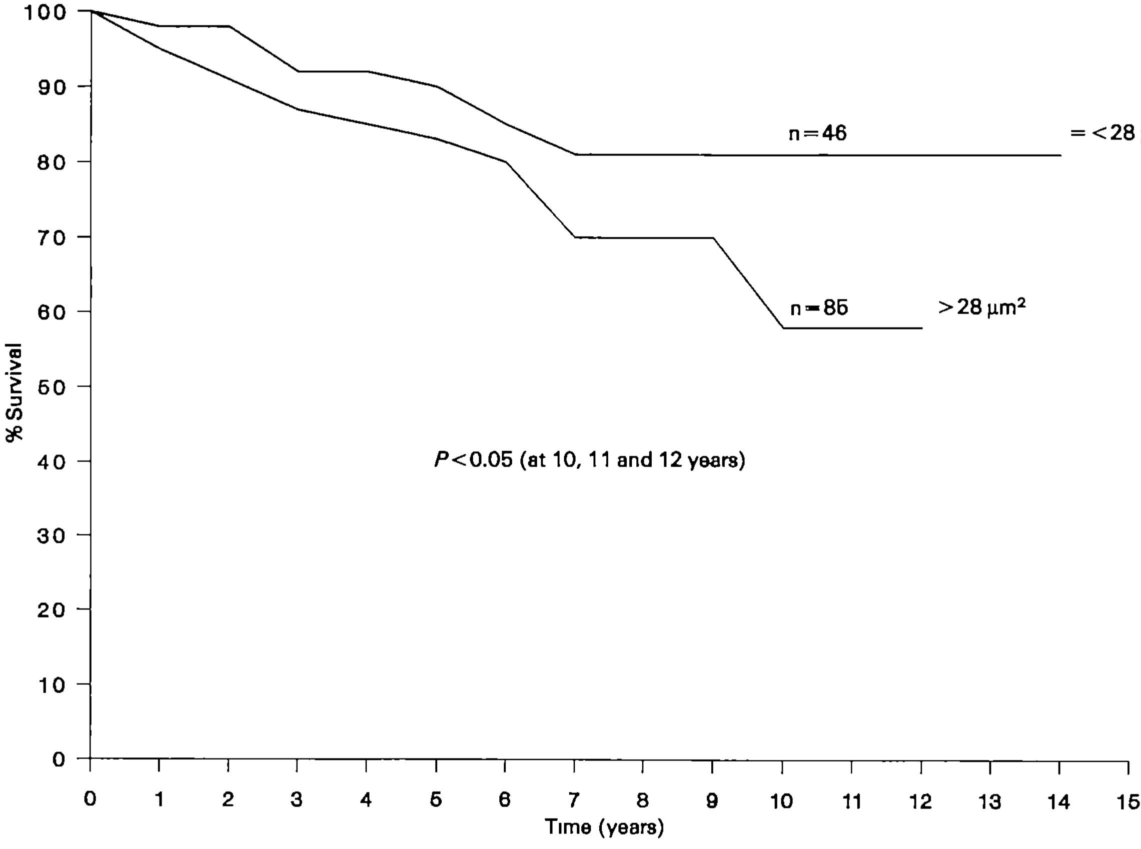

Fig. 2 Survival table for superficial papillary carcinoma in relation to internal zone mean nuclear area $\leqslant$ or $>28\ \mu m^2$.

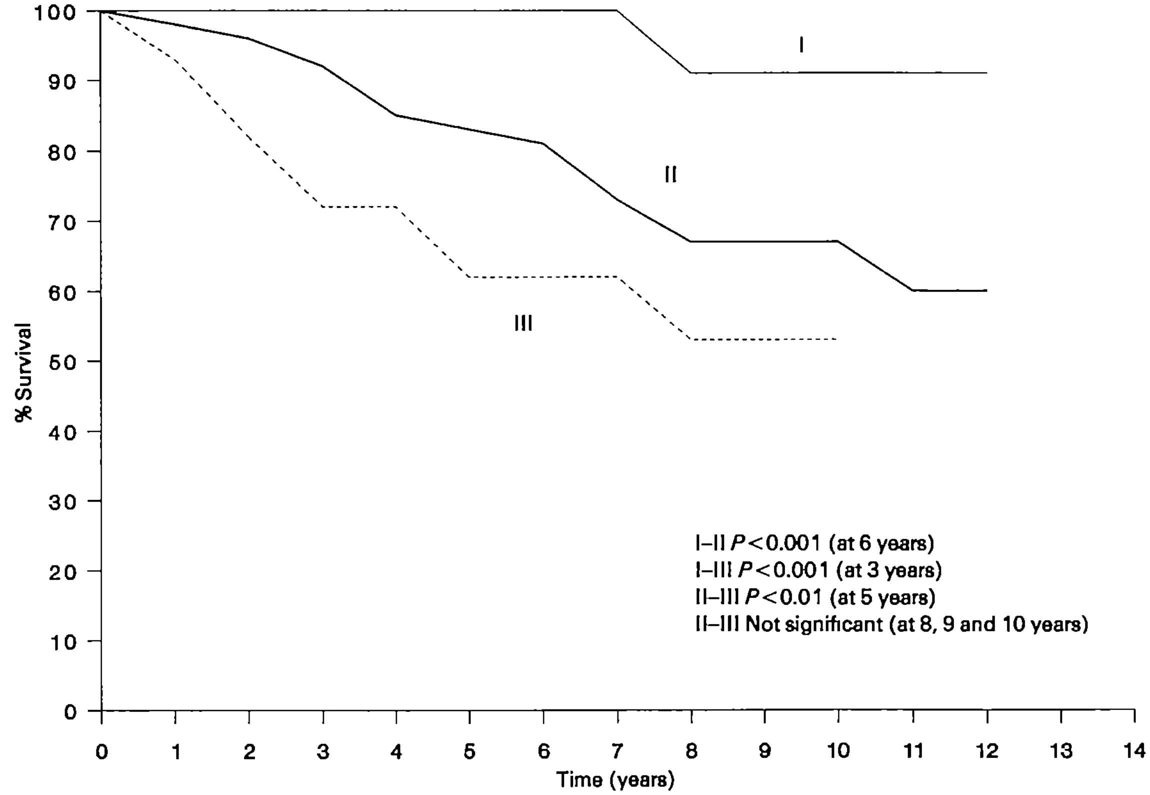

Fig. 3 Survival table for superficial papillary carcinoma in relation to histological grade.

superficial carcinomas, but they measured very selective zones of the tumour.

Vesical tumours can be very heterogeneous, which makes it difficult to assign histological grade by measuring a specific zone. For this reason, Colpaert *et al.* (1987) proposed the measurement of different zones of the tumour, with the final grade being the mean of the grades assigned to each individual zone.

Thus, when they applied morphometry to papillary carcinoma of the bladder, Ooms *et al.* (1983) and Wehner (1986) suggested measuring 3 different zones: the external papillary zone, the internal papillary zone and the largest nuclei regardless of their location. Fleege *et al.* (1988) believed that measuring only large nuclei might introduce a bias into the interpretation of the data, while Helander *et al.* (1985) avoided the measurement of the most superficial nuclei.

Using these criteria as the basis for this study, we measured the external and internal papillary zones. In all, 100 nuclei were measured, applying the general criterion that the more nuclei measured, the greater the reliability of the final result (Hanai *et al.*, 1985; Collan *et al.*, 1986).

We found a higher value for the mean nuclear area of the internal zone than for the external zone. This means that, although the most peripheral nuclei were not measured, there is a tendency for nuclear size to decrease further away from the stroma. This agrees with the findings of Ooms *et al.* (1983) and Wehner (1986).

We also found that the nuclear area value increased with higher histological grade.

In an attempt to discover whether a given nuclear area value might account for a different prognosis in T1 papillary transitional cell carcinoma of the bladder, we found that no significant differences existed using the mean of the 100 nuclei measured. If, however, we considered only the mean nuclear area of the internal zone, we found a better prognosis in those tumours measuring $\leqslant 28\ \mu m^2$.

The results of this study indicate that, in T1 superficial papillary transitional cell carcinoma of the bladder, nuclei close to the stroma should be measured. On the basis of these data, the mean nuclear area may be able to account for a different prognosis. In the present series of 131 tumours, this difference was located around 28 μm². A correlation was also found between nuclear area value and histological grade.

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Prognostic Correlation of Morphometric Values with Survival in Invasive Transitional Cell Carcinoma of the Bladder

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Summary—A morphometric study was made of 95 invasive bladder tumours, differentiating 34 papillary and 61 solid carcinomas. In the invasive papillary tumours, the deeper the zone of the tumour measured, the higher the value of the mean nuclear area. A higher histological grade was also seen to correspond to a higher mean nuclear area value except for Grade IV tumours, whose nuclear area was no larger than that for Grade III tumours. This led us to separate Grade IV tumours from transitional cell carcinomas and classify them as undifferentiated. A better prognosis was found for those tumours whose mean nuclear area was $\leqslant 30\ \mu m^2$ in category T2. For T3 and T4A tumours no conclusive results were obtained in this respect.

Since Ooms *et al.* (1983) and Baak *et al.* (1982) first made their morphometric studies of neoplastic cells, many authors have applied this technique to many different types of tumour. It has been used to study not only tumours of the urinary tract (De Sanctis *et al.*, 1982; Ooms *et al.*, 1983; Montironi *et al.*, 1984; Seldinrijk *et al.*, 1987; Nafe and Frohreberg, 1989) but also other types of neoplasm (Baak *et al.*, 1982; Carter *et al.*, 1989; Payne *et al.*, 1989; Snowden *et al.*, 1989; Lipponen *et al.*, 1990).

Morphometry entails measuring a set of neoplastic cell parameters, particularly those related to the nucleus: area, perimeter, diameter, size and shape factor.

Several studies have demonstrated that nuclear area, perimeter and size show higher mean values according to higher pre-assigned histological grades (Montironi *et al.*, 1986; Van der Poel *et al.*, 1988). It appears to be especially important in differentiating Grade III from Grades I and II.

In this retrospective study, morphometry was performed on the tumour nucleus of a series of invasive transitional cell carcinomas of the bladder in an attempt to correlate the results obtained both with the survival of the patients and with histological grade.

Patients and Methods

From the bladder tumours examined between January 1973 and December 1983, 95 invasive carcinomas were selected. Conditions were that evolution over a period of at least 5 years was known or that death due to the neoplasia had occurred earlier. All patients had undergone radical surgery without adjuvant chemotherapy or radiotherapy.

The classification of Bergkvist *et al.* (1965) was used for histological grading and the series was thus divided into 34 papillary and 61 solid carcinomas.

Using a semi-automatic MOP-VIDEOPLAN image analyser (Kontron, Germany), which consists of a central computer, an image processor and interactive system, together with an OLYMPUS BH2 light microscope and a camera lucida, measurements were made at a magnification of 1000 × of 100 nuclei for each tumour according to the following protocol: in the case of papillary tumours, 25 nuclei were measured from the external papillary

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zone of the tumour, 25 from the internal papillary zone and 50 from the invasive zone; for the solid tumours, 100 randomly selected nuclei were measured but the field was changed so that the measurements were made in different parts of the tumour.

For each nucleus the following parameters were measured: nuclear area, nuclear perimeter, nuclear diameter, nuclear size ($NS = 2\sqrt{}area/\pi$) and nuclear shape factor ($NSF = 4\pi area/perimeter$).

Before measurement commenced, the coefficient of variation (CV) was applied according to the method given by Fleege *et al.* (1988), so that the reliability of the method we were going to use could be assessed. The result was a CV of 1.7, which guaranteed that the method was reliable and, therefore, objective and reproducible.

The statistical analysis was performed with the SIGMA program (Horus Hardware S.A., Madrid, Spain) in a BULL-MICRAL 30 computer.

Results

Invasive papillary tumours ($n = 34$)

Table 1 shows the results of the measurements made in the 3 previously mentioned zones.

To ascertain whether the different parameters for each zone were independent or inter-related, the Pearson correlation coefficient was calculated. A high and significant correlation was found for each group between nuclear area, perimeter, diameter and size (correlation coefficient $= 0.97$), but not always with nuclear shape factor. Because of this high correlation, nuclear area was taken to be representative.

Table 1 shows that the nuclear area is smallest in the external papillary zone and the largest nuclear area corresponds to the invasive zone of the tumour.

Since the correlation between the nuclear area measurements from the external papillary, internal papillary and invasive zones was not very high, a comparison was made of the mean values for the 3 zones taken 2 at a time to establish whether it made no difference which zone was used for measurement or whether, on the other hand, there were differences depending on the zone measured. No differences were found between the external and internal papillary zones, or between the internal papillary zone and the invasive zone, but a significant difference was found between the external papillary and the invasive zones (Table 2).

The overall mean nuclear area for the 3 zones was 45.1493 $\mu m^2 \pm 13.464$.

Nuclear area was also compared in relation to histological grade. The 25 Grade III tumours were seen to have a higher mean nuclear area value than the 9 Grade II tumours, and the difference was significant (Table 3).

Invasive solid tumours ($n = 61$)

Table 4 gives the results of the morphometric study for these tumours.

As with the invasive papillary tumours, the Pearson correlation coefficient was calculated to see if the different morphometric values were independent or inter-related. The correlation coefficient obtained was very high and also significant. In this case we again took nuclear area (mean value 42.7966 $\mu m^2 \pm 13.8162$) as the representative morphometric value.

A comparative multiple-mean test was made according to histological grade and Grade II tumours were found to have a lower mean nuclear area value than Grade III and Grade IV tumours, but Grade IV tumours did not have a larger nuclear area than Grade III tumours (Table 5).

Nuclear area of the 95 invasive tumours

When the 34 papillary and the 61 solid tumours were grouped together, the mean nuclear area was found to be 43.6386 $\mu m^2 \pm 14.951$.

Figure 1 shows the different prognosis of the 95 invasive tumours in relation to their histological grade. Significant differences with regard to sur-

Table 1 Morphometric Values of the Invasive Papillary Tumour (n = 34)

Invasive papillary tumour	*Nuclear area +SD*	*Nuclear perimeter +SD*	*Nuclear diameter +SD*	*Nuclear size +SD*	*Shape factor +SD*
External zone	42.1662	24.1458	8.9161	4.0632	0.87852
	±16.0555	± 4 5274	± 1 6523	± 0.77124	± 0.036623
Internal zone	44 7709	25 2232	9.5052	4.1620	0.88843
	±15.7058	± 4.5497	± 1.7988	± 0.7921	± 0 048639
Invasive zone	48.8101	26.8232	10.6391	4.3233	0.82204
	±18.5216	± 4.6212	± 1.8413	± 0.7842	± 0.057241

Table 2 Comparison of Matched Means between External and Invasive Zones of the Invasive Papillary Tumour

Invasive papillary tumour	*Mean nuclear area*	*SD*	*No. of patients*
External zone	42.1612	16.0555	34
Invasive zone	48.8101	18 5216	34

Difference: −6.6489; Statistical error: 2.7793, $t = -2.3923$; $P < 0.05$.

Table 3 Comparison of Mean Nuclear Area in Invasive Papillary Tumour according to Histological Grade

Histological grade	*Mean nuclear area*	*SD*	*Statistical error*	*No. of patients*
II	35.8258	12.9974	4.3325	9
III	48.6391	12.3316	2.4663	25

Difference: −12.8133, $t = -2.5056$; $P < 0.01$ Significant.

Table 4 Morphometric Values of the Invasive Solid Tumour (n = 61)

Nuclear area +SD	*Nuclear perimeter +SD*	*Nuclear diameter +SD*	*Nuclear size +SD*	*Shape factor +SD*
42.7966 ±13.8162	24 6427 ± 4.3578	9.1672 ±1.5311	4.0969 ±0.7546	0.85601 ±0.037832

Table 5 Comparative Multiple-mean Test of Nuclear Area in Invasive Solid Tumour according to Histological Grade

Histological grade	*Mean nuclear area*	*SD*	*Statistical error*	*No. of patients*
II	28.7329	6.3397	3.1699	4
III	45.3712	16.5354	2.5515	42
IV	39.3383	13.173	3.4012	15

Variable 1	*Variable 2*	*Difference*	*Fisher's f*	*P*
II	III	−16.6383	2.1308	NS
II	IV	−10.6054	0.74856	NS
III	IV	6.0329	0.84779	NS

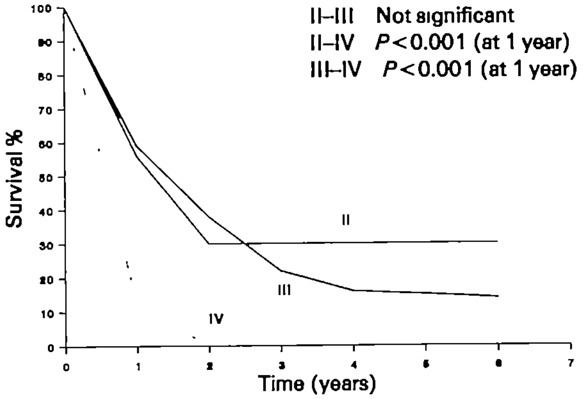

Fig. 1 Survival table for invasive tumours in relation to histological grade

vival can be seen between Grade II and Grade IV tumours, and between Grade III and Grade IV tumours, but not between those of Grades II and III.

When the histological grades were differentiated according to whether the internal zone nuclear area measured ≤ or >30 µm², a better prognosis was observed for Grade II and Grade III tumours whose area was ≤30 µm², and the difference in relation to those with an area >30 µm² was statistically significant. No differences were observed for Grade IV tumours (Fig. 2).

In this complete set, when nuclear area was differentiated according to histological grade, the tumours with the smallest nuclear area were seen to be Grade II tumours, while those with the largest nuclear area were Grade III tumours, larger even than those in Grade IV (Table 6).

An attempt was made to find out if there was a given level for the nuclear area value regardless of stage above which patient survival was different from that of other tumours whose nuclear area did not reach this level.

After a number of actuarial tables had been made, it was found that the T2 invasive tumours with nuclear area values ≤30 µm² showed a survival rate which was significantly higher statistically than those with values >30 µm² (Fig. 3). For T3A tumours, although at the start of the follow-up there were differences, they disappeared as time progressed (Fig. 4). For T3B and T4A tumours, no differences were observed in survival (Fig. 5).

Discussion

The poor prognosis of invasive carcinoma of the bladder regardless of treatment is well known.

The most important prognostic factor for this tumour seems to be category, *i.e.* the extent of the invasion of the vesical wall. Histological grade also appears to play an important rôle (Takashi *et al.*, 1987).

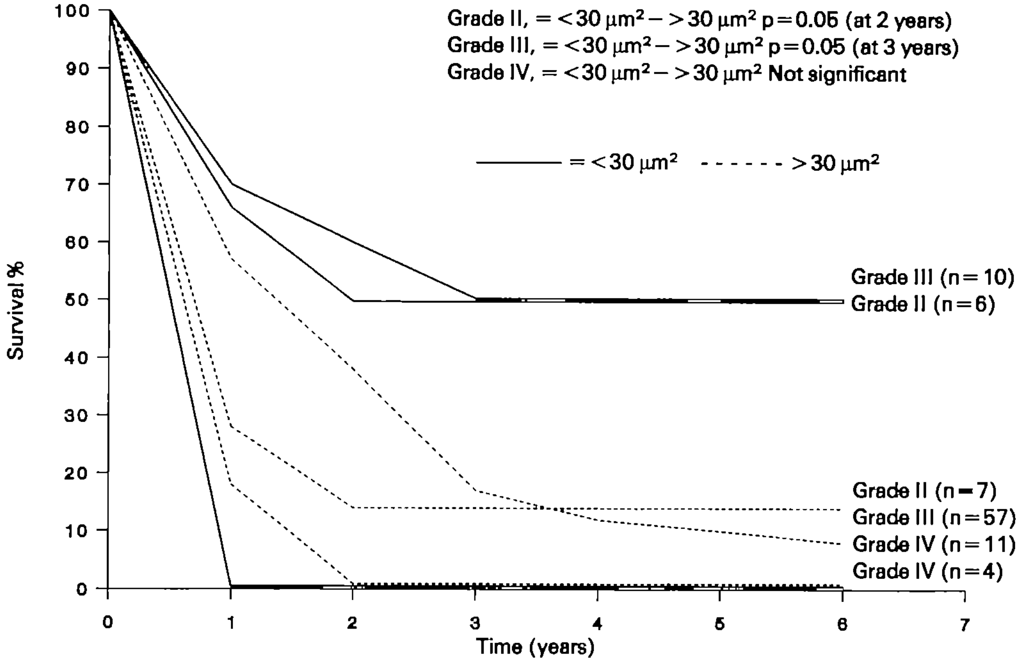

Fig. 2 Survival table for invasive tumours in relation to histological grade and to nuclear area value.

Table 6 Comparative Multiple-mean Test of Nuclear Area in Invasive tumours according to Histological Grade

Histological grade	*Mean nuclear area*	*SD*	*Statistical error*	*No. of patients*
II	33.6433	11.2519	3.1207	13
III	48.0241	15 0058	1.8333	67
IV	39 3383	13.173	3 4012	15

Variable 1	*Variable 2*	*Difference*	*Fisher's f*	*P*
II	III	−14.3808	4.9646	<0.01
II	IV	− 5.6954	1.02196	NS
III	IV	8 6858	1.0465	NS

Nevertheless, there are cases of tumours in the same category, with the same grade and with very similar characteristics, which have a different evolution even though they have been treated in the same way. Is each individual patient's immunological state the decisive influential factor? Is there any other prognostic factor that can be quantitatively evaluated by currently available methods?

Morphometry has been used to differentiate the different histological grades, particularly Grade III from Grades I and II. According to Wehner (1986), Grades I and II only display differences in large cells. On the basis of findings involving the nuclear area, Helander *et al.* (1985) distinguished 2 Grade II subgroups with different prognoses.

Hanai *et al.* (1985) found differences between the nuclear area of normal epithelium and that of Grades I, II and III. However, they found no differences between Grade III and carcinoma *in situ*. Although Smith (1985) reported that nuclear area was useful in establishing subgroups with different prognoses for carcinoma *in situ*, Ooms *et al.* (1983) questioned the value of morphometry in

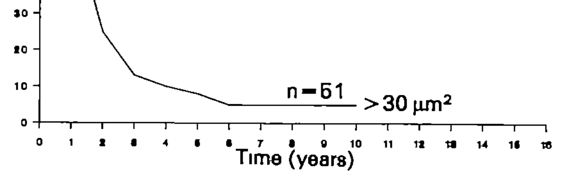

Fig. 3 Survival table for T2 tumours in relation to nuclear area ≤ or >30 μm².

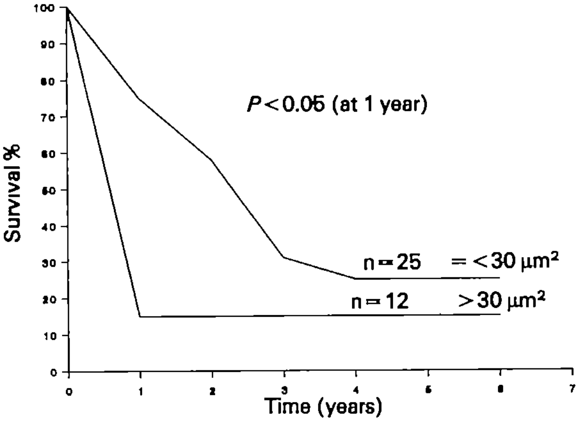

Fig. 4 Survival table for T3A tumours in relation to nuclear area ≤ or >30 µm².

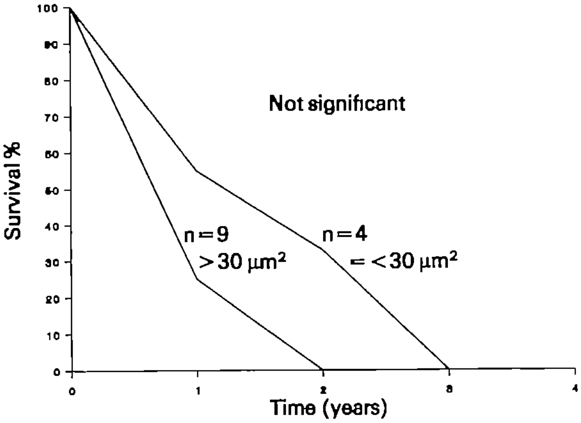

Fig. 5 Survival table for T3B-T4A tumours in relation to nuclear area ≤ or >30 µm²

this particular case since the sample that is generally taken does not represent the whole lesion.

In an attempt to account for the different behaviour of tumours with similar characteristics, our morphometric study of the tumour nucleus was carried out to ascertain whether the results obtained by this method could explain the different evolution of patients in the same category.

The high correlation between nuclear area, perimeter, diameter and size meant that one of them could be taken as representative and used in the correlation with survival. We chose nuclear area, as have other authors (Van der Poel *et al.*, 1988).

For the 34 invasive papillary tumour we followed the recommendations of Ooms *et al.* (1983), Helander *et al.* (1985), Wehner (1986) and Colpaert *et al.* (1987), who suggested measuring different zones of the tumour and taking the mean values. Our results indicated that the external papillary zone had the lowest nuclear area value and showed a significant difference with respect to that of the invasive zone of the tumour. The mean value for the 3 zones was 45.1 µm² and Grade III tumours had a larger nuclear area than Grade II tumours.

The 61 invasive tumours had a mean nuclear area of 42.7 µm². Although Grade III tumours had a larger nuclear area value than Grade II tumours, the mean nuclear area of those in Grade IV was not larger than the Grade III tumour value. This may be because one of the characteristics of undifferentiated tumours is that they have primitive nuclei, which are not necessarily large.

Since the mean nuclear area values of the invasive papillary tumour (45.1 µm²) and the invasive solid tumour (42.7 µm²) were not significantly different, the 2 types of tumour (n=95) were grouped together; all of them were muscle-invasive and the overall mean nuclear area was 43.6 µm².

When all of the invasive tumours were taken together, Grade II tumours were still seen to have the smallest nuclear area and Grade III tumours the largest, larger even than those of Grade IV. This information justified separating Grade IV from the rest of the transitional cell carcinomas and classifying them as undifferentiated.

A better prognosis was found for Grade II and Grade III tumours with a nuclear area ⩽30 µm² than for those whose nuclear area measured >30 µm² and this difference was statistically significant. Owing to their poor prognosis, this difference was not found for Grade IV tumours.

The correlation of nuclear area with survival within the same category showed that the 5-year survival rate for T2 tumours with a mean nuclear area ⩽30 µm² was 53%, whereas for those with a value >30 µm² the rate dropped to 7%. After 10 years' follow-up the difference was maintained, with survival rates of 45 and 5% respectively.

Survival at 2 years for T3A tumours with a mean nuclear area ⩽30 µm² was 58% compared with only 16% for those with a value >30 µm². However, after 5 years' follow-up there was no statistically significant difference. For categories T3B and T4A it was practically impossible to establish differences because of their poor prognosis and also because of the low number of cases of tumour with a mean nuclear area ⩽30 µm².

The following final conclusions can be drawn. Firstly, there is a high correlation between all of the morphometric values measured with the exception of shape factor. The values, therefore, were not independent.

Secondly, there is a correlation between histological grade and mean nuclear area, with the latter increasing from Grade II to Grade III. Since Grade IV does not give a higher value for mean nuclear area than Grade III, we suggest, as has been done in other classifications, that Grade IV tumours should be separated from transitional cell carcinomas and should be classified as undifferentiated.

Finally, a better prognosis was found for those T2 tumours with a mean nuclear area $\leqslant 30\,\mu m^2$. Our results for T3 and T4A tumours were not conclusive in this respect.

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Clinical Information System that Enhances the Use of Resources in Endoscopic Prostatic Procedures

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Summary—In this study we evaluated, by means of an automated management system, the identification of subgroups of patients within certain operative categories whose predictable length of stay was compatible with treatment on a 5-day ward. This was achieved by using a computer directed analysis of urological workload on prospectively collected clinical data. Graphical presentation of the results was achieved by a technique known as the patient-bed dissociation curve.

Patients with bladder outflow obstruction treated by transurethral prostatic resection (701) and bladder neck incision (113) were selected from a total of 7162 hospital admissions. The main outcome measures were length of stay and complication rates for the 2 procedures.

The results demonstrated that a group of patients about to undergo transurethral resection could be selected by age and source which would indicate an 18% greater probability of discharge within 5 days. These patients were easily identifiable in advance and would be suitable for treatment on a 5-day ward.

It was concluded that computer-held clinical data were easily accessible to the surgeon. The process of detailed analysis need not take time. With properly directed studies the information retrieved could be used to effect change. The patient-bed dissociation curve may prove a valuable tool in examining and comparing discharge patterns in any groups of patients.

Surgeons have been using microcomputers for clinical audit and patient administration since the early eighties. Following publication of the initial reports (Ellis *et al.*, 1987; Dunn, 1988), automated management systems have been incorporated into the running of many surgical departments in this country. During this time over 90 different systems have been used; a small number of software systems account for most of the implementations.

One of the factors fuelling this trend has been the growing scepticism concerning the validity of hospital-held data (Skinner *et al.*, 1988). Although some concerns regarding the completeness of data held on microcomputers have been raised (Lyons and Gumpert, 1990), there is a general consensus that the quality of data gathered by clinicians on their own workload is superior.

The full potential of this growing database has not been realised. Most of the systems in hospital practice are used primarily for the efficient retrieval of unprocessed clinical data, as in the generation of discharge summaries, the provision of an up-to-date and instant "patient status", waiting list management and the production of coded reports for hospital administration systems. The other area in which these systems perform is the production of activity analysis data. In its ability to produce a breakdown of admissions, discharges, length of stay, *etc*, the computer is unmatched. This function alone has made the process of clinical audit a practical proposition (Ellis and Sensky, 1991).

Much of the literature over the last 5 years has described the methods of implementing computer systems and how best to present and use the data obtained (Lyons and Gumpert, 1990). There has been little attempt to harness the power of these

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systems for clinical research (Ellis, 1991a). Until recently, the computer's function as a research tool was simply to identify particular patient populations, whether by age, operation or diagnosis. This represents insufficient use of the investment made in acquiring these databases, both in capital expenditure and input time.

The present report illustrates how computer-held data can be used to address a specific clinical question in a district general urological practice. The information obtained was used to effect change in the way patients were managed.

Materials and Methods

The management system

In 1985 we began to collect data on to a *MICROMED* surgical management system (Medical Systems Ltd) designed by clinicians in association with computer professionals (Ellis *et al.*, 1987). Although all 3 surgical firms now enter their clinical data on to the system, the information obtained for this study represents the clinical activity of a single firm or team of 1 consultant, 1 registrar and 1 preregistration houseman. When the system was set up, data were entered retrospectively to September 1984. This study was directed at the clinical activity from September 1984 to February 1991 inclusive.

The setting

The study was based on the analysis of the workload of that single firm for a period of 5 years in a district general hospital. The consultant firm under study has a 1 in 3 general surgical on call commitment. The routine work is mixed general surgery and urology. The urological component has been increasing over the years. Only the urological workload was subjected to analysis.

The clinical problem

We had become aware that there was a persistent under-use of the short stay unit for endoscopic bladder and prostate procedures. The unit is partly day care and partly a 5-day ward, *i.e.* half of the beds are open from Monday 0800 to Friday 1700 and the other half are used for day care only. Furthermore, bed allocation to the general surgical ward at the beginning of the week was becoming increasingly difficult.

A significant proportion of younger men who were to have a bladder neck incision (BNI) as a planned procedure for bladder outflow obstruction were being admitted to the 5-day ward. It is known that such patients usually have a short hospital stay with a low complication rate (Edwards *et al.*, 1985). However, these patients represent only a small proportion of those who need an endoscopic procedure for outflow obstruction. To enable us to use the spare bed capacity on the 5-day ward we would have to identify a group of patients from an operation that was commonly performed. This proved to be transurethral resection for benign prostatic hypertrophy (TURP). It was our initial impression that this group of patients would not be ideally suited to short stay. They are elderly, have a high incidence of co-morbidity, and many live alone. Would it be possible to identify a group of patients from this population who would have a high probability of discharge within 5 days of admission?

Since bed allocation takes place shortly before admission, without the patients' case notes, and often by a medical secretary, an easily identifiable predictor of length of stay was required. To identify such a predictor more information was required on the population of patients undergoing endoscopic prostatic procedures.

The analysis

The primary analysis was to identify the patient populations by operation. This information was retrieved on the *MICROMED* system by using the analysis function. Two groups (BNI and TURP) were identified from 7162 admissions. It was then possible to "save" them on the computer for a more detailed analysis. The 3 forms of analysis to which the 2 populations were subjected were age distribution, length of post-operative stay and complication rate.

The results obtained from the first 2 forms of analysis were converted to chart form and bar charts were constructed using Harvard Graphics software (Figs 1 and 2).

To answer the specific clinical question on the use of a short stay ward for the purposes of TURP a different form of graphical interpretation was required. This we have called the *patient-bed dissociation curve* (Fig. 3). The curve starts with 100% bed occupancy on the first post-operative day and then shows the rate of discharge over time. From the length of post-operative stay of each patient it is possible to calculate the number of patients in each group who were discharged on each post-operative day. A cumulative total shows how many patients were discharged by each post-operative day (Table 1). From the cumulative totals it is possible to calculate the percentage of patients

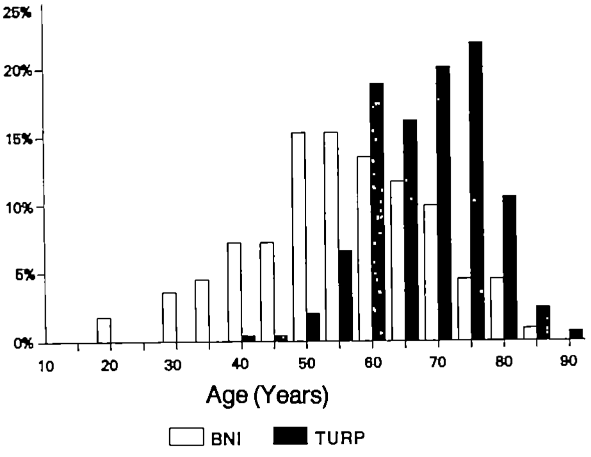

Fig. 1 Age distribution by procedure.

Table 1 Distribution of Stay Length by Operation

Post-operative stay (days)	*BNI*	*TURP (all)*	*TURP (selected)*	*TURP (rejected)*
1	17	6	1	5
2	46	22	10	12
3	83	75	51	46
4	97	296	141	155
5	99	490	211	279
6	102	566	234	332
7	106	608	248	360
8	109	638	258	380
9	109	653	259	394
10	109	660	261	399
11	109	678	264	414
12	109	685	266	419
13	110	694	268	426
14	110	697	268	429
Totals	112	738	271	467

discharged at any point in the post-operative period. The percentage bed occupancy can thus be deduced.

Results

The age distribution of the 2 groups of patients (BNI and TURP) is illustrated in Figure 1. It is clear that the populations who underwent prostatic resection are quite distinct from those who underwent bladder neck incision.

Figure 2 shows the percentage of patients in each operative group who stayed for a given number of days after operation. It supports our clinical impression that bladder neck incision is associated with a shorter length of stay than TURP. This form of chart presentation is satisfactory for revealing such a difference.

In Figure 3 the same data were used to construct a patient-bed dissociation curve. It is clear that by the fifth post-operative day one-third of the TURP group will still be in hospital. Both curves in Figure 3 exhibit parallel lines in the middle section of the curve. This corresponds to the rate of discharge, which is similar in both populations, albeit 2 days later in the TURP group. The characteristics of the curve begin to change as length of stay increases. There is a greater proportion of long stay patients in the TURP group. These observations cannot easily be made from Figure 2.

Selecting patients for early discharge

Perusal of length of stay data by age suggested that above the age of 70 years a greater proportion of patients stayed in hospital for more than 5 days.

Similarly, patients not admitted on an elective basis from the out-patient department also had a longer stay, probably because more of them had indwelling urethral catheters or co-morbidity when admitted through Accident and Emergency by referral or by a planned "readmission". Thus the computer system was used to identify those patients who had undergone TURP, who were aged 70 or less, and whose source of admission was from the out-patient department. They were known as the TURP-selected group. It was felt that they were likely to have a shorter length of stay than the rest of the TURP group and that they would be easily recognisable in advance. The TURP-rejected group included all of the remaining patients who underwent TURP. The patient-bed dissociation curve (Fig. 4) shows the pattern of percentage bed occupancy for 3 groups of patients. The BNI group shows a steeply falling curve as patients are discharged on the first and second post-operative day. The TURP slopes take 2 to 3 days before the rate of discharge approximates that of the BNI group. The TURP-selected group shows a different pattern of discharge from that of the TURP-rejected group. On the fifth postoperative-day in the selected series the occupancy rate was 22%. This compares favourably with an occupancy rate of 34% in the unselected group (χ^2 correlation for continuity=24.4, $P<0.001$, 18% difference in rate of discharge. Confidence limits, 95% probability that the difference in rate of discharge is between 11.5 and 24.8%). Of all 738 TURP episodes 271 matched the criteria for short stay and 476 did not.

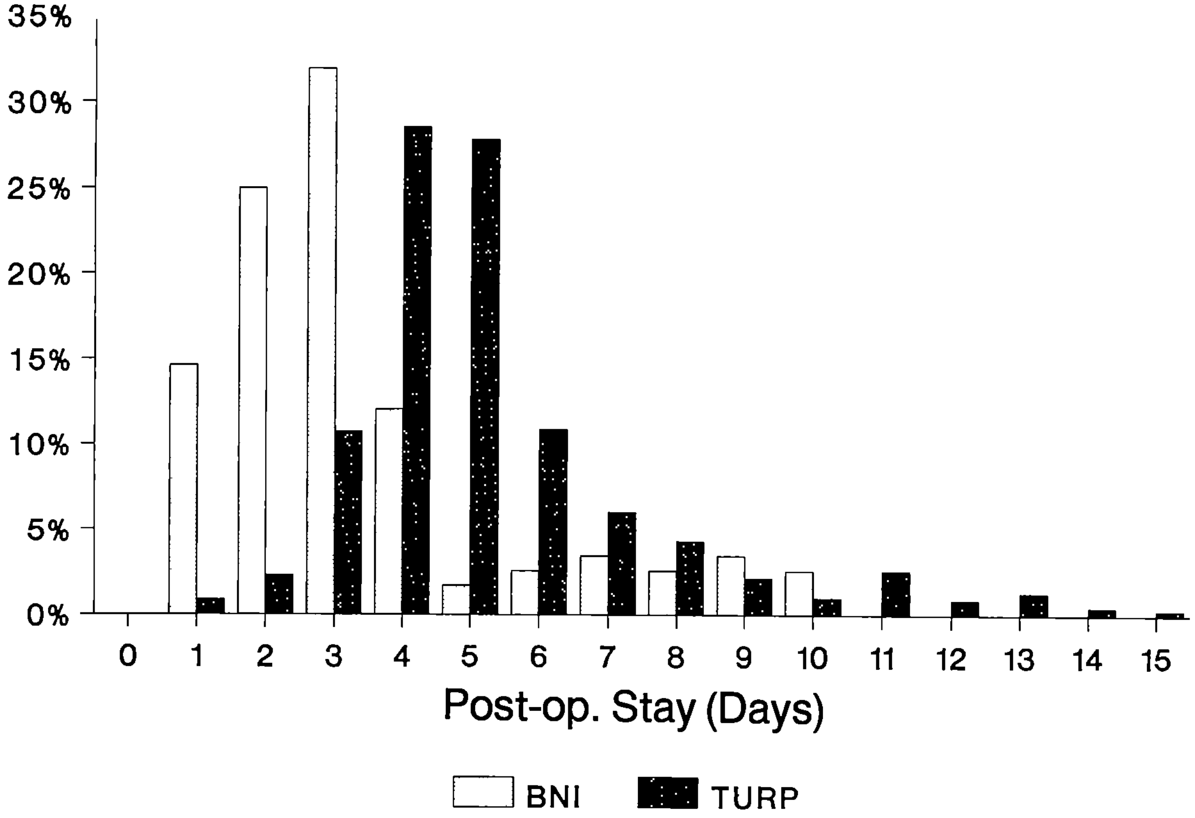

Fig. 2 Post-operative stay by procedure.

Although not directly applicable to the pattern of discharge in the first 5 days, it is interesting to note that by selection on age criteria and source of admission the pattern of discharge in the TURP population after 5 days changes considerably. The proportion of long stay patients is considerably reduced, so that it follows the pattern of those patients who underwent bladder neck incision (Fig. 4).

Discussion

Since Sargent (1934) noted the superiority of the 16-day hospitalisation and $101 hospital bill using

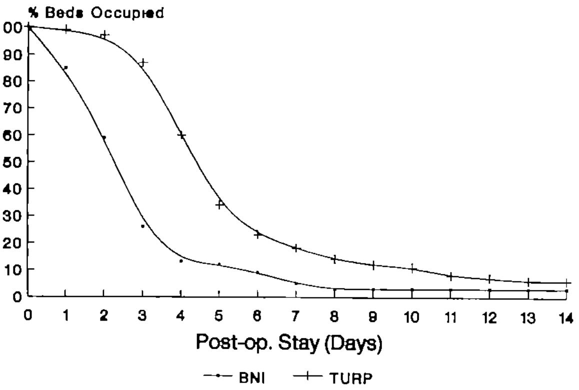

Fig. 3 Patient-bed dissociation curve to compare bladder neck incision (BNI) with transurethral resection of the prostate (TURP).

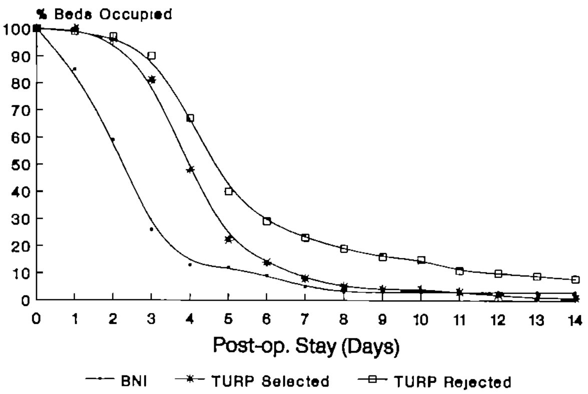

Fig. 4 Patient-bed dissociation curve to illustrate the effect of selecting TURP patients for short stay at 5 days. There is a significant difference ($P<0.001$).

the transurethral approach compared to the 30-day stay and $188 cost of a suprapubic operation, surgeons have attempted to reduce the hospital stay after prostatectomy.

The direct link between cost and post-operative stay was addressed in a study which analysed the factors influencing cost in elective colorectal operations (Arabi *et al.*, 1980). It was concluded that the duration of hospital stay was the single most important determinant of cost. In an attempt to determine which factors influenced post-operative stay after TURP, Wolverson *et al.* (1986) studied 12 clinical and social factors. Only 3 factors were found to be predictive: age, concomitant vascular disease and weight of the prostate gland. Since none of these factors could be modified by the physician, it was concluded that length of stay was not likely to be further reduced.

We have not tried to address the threshold problem of defining scientific criteria for operation. Any study concerned with the issue of cost in prostatectomy should consider the work of McPherson *et al.* (1982), in which the rate of prostatectomy per 100,000 population varied from 264 in New England to 133 in the Midlands. The differences were due more to the habits of physicians than to scientific sophistication or administrative systems (Angell, 1985).

What this computer analysis has shown is that it is possible to improve efficiency by identifying subgroups of patients, within operative categories, who can be managed in a more cost-effective manner. This method of analysis is directly applicable to any commonly performed operation (Ellis, 1991a). For the purposes of planning it is important to appreciate that patients undergoing an identical operation are not a homogeneous group. Within each operative category patient groups can be identified and their clinical course assessed.

We believe that the patient-bed dissociation curve (Fig. 3) allows a clearer comparison of the length of stay pattern between 2 treatments than a simple bar chart (Fig. 2), even though the latter is considerably more revealing than a column of figures (Table 1). It is easy to see at what stage any given proportion of patients will be ready for discharge. In addition, it permits estimation of the extra provision that will have to be made to accommodate patients who are not ready for discharge on a given day. This method of displaying discharge rates makes it easy to see when half of the patients are home and what proportion is left in hospital on any given post-operative day. This figure also helps in assigning a predictive discharge rate to previously defined patient populations. Since hospital stay in TURP is the most significant factor in influencing cost, the predictive discharge rate will be an indication of the costing characteristics in each selected group.

While this type of charting has, so far, only been used in this particular case we would suggest that some of the characteristics of the curve may give further insight into the discharge pattern of patients. Thus the gradient of the steepest part of the slope may indicate the consistency of length of stay for most patients, while the gradient of the tail of the curve will reflect the ease with which the problems of patients with complications or other medical or social problems can be resolved.

When considering aspects of cost-containment it is fundamental to ensure that patient care does not suffer. Most externally imposed methods of cost reduction are not in the patient's best interest. These methods are relatively crude, achieving their aims by ward closures or waiting list constraints (Ellis, 1991b). It is also important that the doctor/patient relationship is not compromised when the physician assumes the role of rationer (McPherson *et al.*, 1982). With this use of computer-derived data the clinician can be reassured that patient outcome will not be affected. The analysis has considered patients who have had standard practice. The patients will continue to have standard practice as no modifications to patient care have been implemented. By channelling the patients who are likely to have an early discharge into a 5-day ward, both an increase in throughput and a potential unit cost reduction are achieved.

This approach is at variance with attempts to reduce hospital stay and therefore cost in the United States. Sage *et al.* (1988) showed that there was considerable variation in practice amongst surgeons performing prostatectomies. By investigating these variations by means of "cost-effective" orientated meetings they reported changes in practice with cost savings and no observed reduction in quality of care. In effect, what they were doing was clinical audit. Application of these methods will help to reduce the wasteful practices that were the principal findings by Sage *et al.* (1988) in terms of the number and type of investigations requested and pre-operative length of stay.

When considering resource implications from a retrospective method of data analysis it is important to be aware that ward practice has changed substantially since this type of computerised data collection was started in the mid-eighties. Much of the data relevant to this study was collected at a time when there was little, if any, constraint on beds. The length of stay for all operations at Ashford Hospital has been reduced by 24% since 1984. It is also likely that the length of stay for the endoscopic procedures analysed in this study has also been reduced since the introduction of externally imposed bed constraints. If this is so, an evaluation of recent length of stay would show an improved performance as measured by stay length criteria. Performance indicators cannot stand alone in the assessment of workload; some measure of outcome is needed to ensure that treatment objectives are realised. As a guarded quality index we have included complication rates and mortality on the populations studied (Table 2). These complication rates are produced automatically by the computer. Although a crude guide to assessing outcome, easily accessible complication rates help to provide an ongoing method of quality control. An outcome measure that incorporates both the patients' and the doctors' objectives does not yet exist. It is this area that needs attention if medical audit is to have any useful role in future health care evaluation.

Table 2 Complication Rates by Operation

	TURP (738)	*BNI (112)*
Respiratory		
Sputum retention	3	
Pneumonia	6	
Respiratory arrest	1	
Other	1	
Cardiovascular		
Arrhythmia	7	
Myocardial infarction	3	
Cardiac arrest	1	
Hypovolaemic shock	1	
Septicaemic shock	2	
Other	2	
G-U and renal		
Urinary tract infection	53	3
Retention (post-op)	21	3
Haematuria	10	
Clot retention	11	
Incontinence	3	1
Other	3	
Nervous system		
Confusion	10	
Depression	2	
CSF leak	1	
Other	3	1
Miscellaneous		
Septicaemia	7	
Clotting disorder	1	
Unexplained fever	1	
Other	3	
Total	156	8

Deaths: 1 TURP myocardial infarction (85 years), 1 BNI bronchopneumonia (72 years)

A study such as this, which is economical to undertake, that can be completed in 1 day using only 1 person's time, will help to identify subpopulations of patients who can be managed in a more cost-effective way. The ease with which information can be retrieved can turn a 6-month study into an afternoon exercise. The information obtained can be used to effect change. The use of novel tools such as the patient-bed dissociation curve may make these large amounts of data more meaningful to the end user. More specifically, the patient-bed dissociation curve may prove valuable in defining discharge probabilities for groups of patients. Once these probabilities are known for each easily identifiable population of surgical patients, the prediction of bed usage should become a less haphazard undertaking. The application of this technique to other procedures and other patient populations should provide useful information for resource planning.

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Phase II Study of Epirubicin in Advanced Hormone-resistant Prostatic Carcinoma

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Summary—Twenty-nine patients with metastatic prostate cancer that had progressed following orchiectomy were treated with intravenous epirubicin 90 mg/m^2 every 28 days. Their median age was 71 years (range 49–78) and the median Zubrod scale (WHO score) was 1. Two patients had soft tissue lesions, 20 had bone metastases and 7 had both. Tumour response was assessed according to the National Prostatic Cancer Project criteria. Of 29 patients, 11 (38%) achieved a partial remission. The median duration of response was 6 months and the median survival time of all patients was 9 months (range 2–27). It seemed that treatment with epirubicin was not associated with an increase in survival. Toxicity was moderate and consisted of alopecia and mild nausea/vomiting. There was no significant haematological toxicity and no clinical cardiotoxicity. It was concluded that epirubicin was active in hormone-resistant metastatic prostate cancer in approximately 33% of the patients.

No effective treatment exists after hormonal failure in advanced prostate cancer. Chemotherapy is advocated by some, but must still be considered experimental. Subjective improvement may be achieved but objective partial responses occur in only 20 to 30% of patients, without measurable impact on survival. Combination chemotherapy does not appear to be superior to single agents. Doxorubicin can be regarded as one of the single drugs with reported activity. Because of the better therapeutic index of epirubicin, it appeared worthwhile to assess this drug. Tolerance of therapy and decreased cardiotoxicity are particularly important in these patients, who are usually elderly and often have concomitant cardiovascular disease.

Patients and Methods

Eligibility criteria included metastatic prostate carcinoma that progressed following orchiectomy, age less than 80 years, performance status (WHO score) 0–2, normal radioisotope left ventricular ejection fraction and adequate general condition. Treatment consisted of intravenous epirubicin 90 mg/m^2 every 4 weeks. Treatment was withheld in the case of >grade 1 haematological toxicity on the scheduled day of treatment.

Response in patients with bone metastases was assessed according to the criteria of the National Prostatic Cancer Project, *i.e.* partial response in the case of $\geq 50\%$ reduction in areas of increased uptake on radioisotope bone scans, with $>50\%$ decrease in acid phosphatase and no new sites of disease. In patients with soft tissue lesions the WHO criteria were used, *i.e.* partial response in the case of a 50% reduction in the sum of the products of the largest perpendicular diameters of measurable lesions for at least 4 weeks. Patients with both soft tissue and bone metastases who showed a response in soft tissue without progression in bone metastases were classified as a partial response. The duration of partial response and of survival was measured from the start of treatment.

A total of 29 patients entered the phase II study and all were fully evaluable. Their median age was 71 years (range 49–78). Their median performance status was grade 1 (range 0–3). Twenty patients had only bone metastases, 2 only soft tissue lesions, and 7 had both.

Results

There were no complete responses. Eleven patients (38%) achieved a partial response. Of 9 patients with soft tissue lesions 5 (55%) responded, while of

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20 patients with only bone metastases 6 (30%) achieved partial remission. All responders experienced clear subjective improvement. Three of the 6 responders with only bone metastases had normal acid phosphatase. The median duration of response was 6 months (range 3–19). Transient relief of symptoms was observed in 14 patients (48%). It was remarkable that obvious symptomatic relief occurred in 3 patients who did not show any objective response. Bone pain—a major symptom in 26 patients—diminished in 13 cases (50%). The symptoms of general malaise, present in 5 patients, disappeared in 3 cases. In general, the WHO performance scale improved in approximately one-third of patients. With the exception of alopecia, toxicity was moderate and all patients were ambulatory. The median number of cycles was 6 (range 1–12). There was no significant haematological toxicity. Nausea/vomiting was grade 1–2 only. There was no clinical cardiotoxicity. All patients have now died. Their median survival was 9 months (range 2–27) (Fig.).

Discussion

The response in this trial is within the confidence limits of that reported with doxorubicin and other single agents (Jones *et al.*, 1986). Doxorubicin has been assessed in several phase II and III studies as a single agent and in combination chemotherapy. Response rates ranged between 0 and 50%. In particular, a weekly "low-dose" schedule has aroused interest. In 2 studies an objective response rate of 16% or improvement in 84% of 25 patients was reported (Torti *et al.*, 1983), or good symptomatic improvement in 10 of 21 patients (50%) (Robinson *et al.*, 1983). However, Fosså *et al.* (1987) found no objective responses with weekly doxorubicin in 21 patients. Epirubicin in a low-dose weekly schedule of 12 mg/m^2 has been assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Urological Group. There was a 12% response rate with 42% stabilisation in 33 evaluable patients with soft tissue, liver or lung metastases as indicator lesions (Jones *et al.*, 1987).

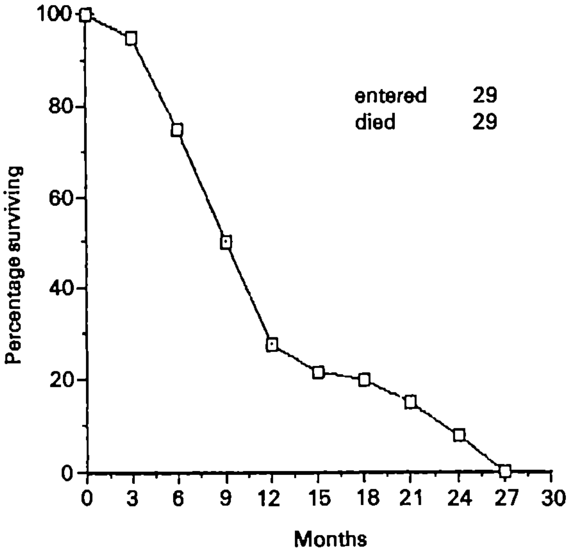

Fig. Survival of all patients.

The difficulty in measuring response in patients with osteoblastic bone metastases is well recognised. The response rate in the present study might be regarded as inflated because we modified the criteria developed by the NPCP and qualified a 50% reduction instead of normalisation of the tumour marker in patients with bone metastases as a partial response. With strict criteria, however, the overall response rate was 28%. Thus epirubicin can produce responses with acceptable toxicity in patients with metastatic symptomatic prostate cancer refractory to hormonal manipulation. The optimal administration schedule and comparison with other treatment options in these patients require comparative studies.

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Rectal Obstruction Secondary to Carcinoma of the Prostate Treated by Transanal Resection of the Prostate

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Summary—Rectal obstruction caused by carcinoma of the prostate is uncommon. If the disease does not respond to either hormonal treatment or radiotherapy, the only surgical means of relieving the obstruction has been the formation of a colostomy. We present an alternative treatment, since many of these patients are elderly with a short life expectancy and they may have difficulty coping with a stoma. Seven transanal endoscopic resections of the prostate (TARP) have been performed on 5 patients. The procedure is not without complications, but it does offer simple surgical palliation of the rectal obstruction and obviates the need for a colostomy.

Rectal involvement by prostatic carcinoma is uncommon. Lasser (1978), in a review of the literature, reported an incidence of 0.5 to 0–9%. Saitoh *et al.* (1984), in a review of 1367 autopsy cases with prostatic carcinoma, found 126 patients with rectal involvement, an incidence of 9.4%. The clinical difficulties in distinguishing this condition from a primary rectal carcinoma, whose management is different, have been discussed by other workers (Winter, 1957; Lasser, 1978; Siegel *et al.*, 1986; Foster and O'Reilly, 1990). Lazarus (1935) classified prostatic carcinoma with rectal involvement into 3 groups; in type 1 a large tumour protrudes into the rectum and occludes it. In type 2 the tumour encircles the rectal wall, causing a stenosing, annular lesion, and in type 3 the rectal mucosa is directly invaded by the tumour and may have features of the other 2 groups (Fig. 1). Winter (1957) added 2 further groups to this classification: type 4, separate metastases to the rectosigmoid, and type 5, a synchronous carcinoma of the rectum.

One of the clinical manifestations of this condition is rectal obstruction. Because the disease is often advanced by the time of presentation, palliative treatment is all that can be offered. The majority of tumours will respond to hormonal therapy (Winter, 1957; Foster and O'Reilly, 1990) but if this fails, radiotherapy to the obstructed rectum may provide satisfactory palliation (Green, 1974; Siegel *et al.*, 1986). In patients who fail to respond to either hormonal or radiation therapy, a colostomy may be necessary to relieve the intestinal obstruction (Lazarus, 1935; Mir *et al.*, 1973; Fry *et al.*, 1979).

Zinkin *et al.* (1979) first described the technique of palliative resection with the urological endoscopic resectoscope for obstructive low lying primary rectal tumours. Since then, several authors have confirmed its value in the treatment and local control of low lying benign and malignant rectal lesions (Weese and Bruskewitz, 1984; Sosa and Pitts, 1988; Kelly, 1989; Vaccaro *et al.*, 1990). Sosa and Pitts (1988) also performed palliative transanal resections of pararectal tumours, although the source of these tumours was not reported. We present our experience with the technique of transanal resection in the palliation of symptomatic rectal obstruction secondary to carcinoma of the prostate.

Patients and Methods

Between 1990 and 1991, 7 transanal resections were performed on 5 patients with symptomatic rectal

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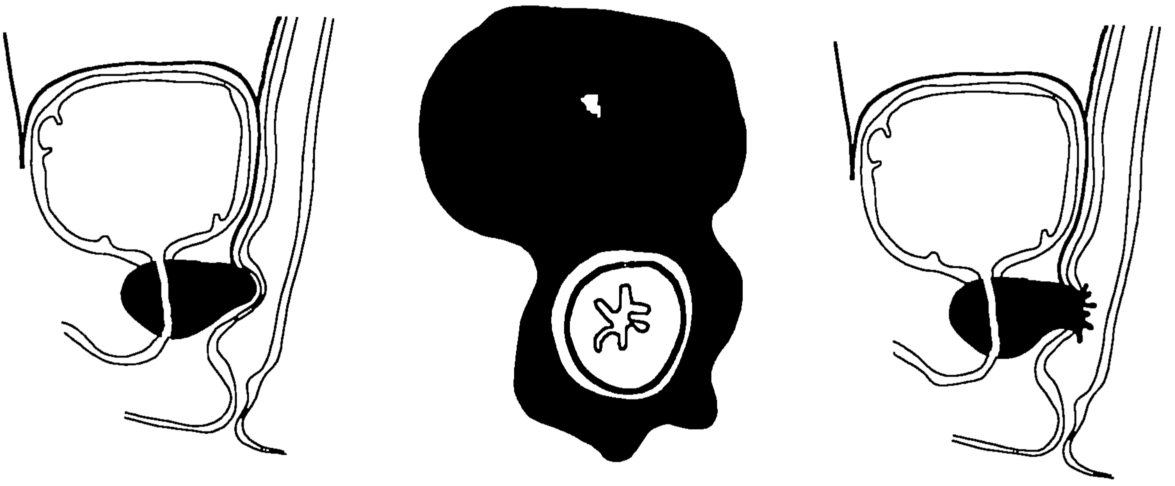
Read at the 48th Annual Meeting of the British Association of Urological Surgeons in Bournemouth, June 1992



Type 1 Type 2 Type 3

Fig. 1 Classification of prostatic carcinoma with rectal involvement.

obstruction secondary to carcinoma of the prostate. All 5 patients complained of constipation, tenesmus and, in 2 cases, rectal bleeding (Table 1). The mean age of the patients was 78.8 years (range 71–90). All had previously undergone hormonal manipulation and one patient also received palliative radiotherapy to the obstructed rectum. Digital rectal examination and sigmoidoscopy were found to be adequate for assessing the type of rectal involvement. Three patients also had pelvic CT scans. The CT scan appearances of type 1 and type 2 rectal lesions are shown in Figure 2.

While bowel preparation was not used because of the occlusive nature of the tumour, prophylactic antibiotics (600 mg benzylpenicillin, 80 mg gentamicin and 500 mg metronidazole) were routinely given peri-operatively for 24 h.

All patients were placed in the standard lithotomy position under general or spinal anaesthesia. A standard 3-litre bag of 1.5% glycine solution was used for irrigation. A Storz 24 F sheath urological resectoscope with a 30° telescope was passed into the rectum. The tumour bulk was resected with the cutting loop or, in the case of annular constricting lesions, a channel was created. Where the obstruction was due to an anterior protrusion by the malignant prostate, the sweeps of the cutting loop were directed towards the tumour bulk (Fig. 3). Sufficient prostatic tumour was resected to allow the passage of 3 fingers across the rectal stenosis. Once rectal muscle fibres were seen, resection in that area was stopped in order to prevent perforation of the rectum. Haemostasis was obtained with a ball coagulating diathermy. The large capacity of the rectum and sigmoid colon allowed almost continuous resection in a low pressure system.

Table 1 Clinical Details

Patient no.	*Age (years)*	*Type of stricture*	*Bony metastases*	*Upper tract obstruction*	*Hormonal therapy*	*Radiotherapy*	*Past medical history*
1	81	3	Yes	Yes	Cyproterone acetate	No	
2	78	2	Yes	No	Orchiectomy. Cyproterone acetate	No	Deep vein thrombosis and pulmonary embolism
3	90	1	No	No	Cyproterone acetate	No	Hypertension
4	71	2	No	Yes	Cyproterone acetate + goserelin acetate	No	Angina
5	74	3	No	Yes	Cyproterone acetate + goserelin acetate	Yes	Myocardial infarction

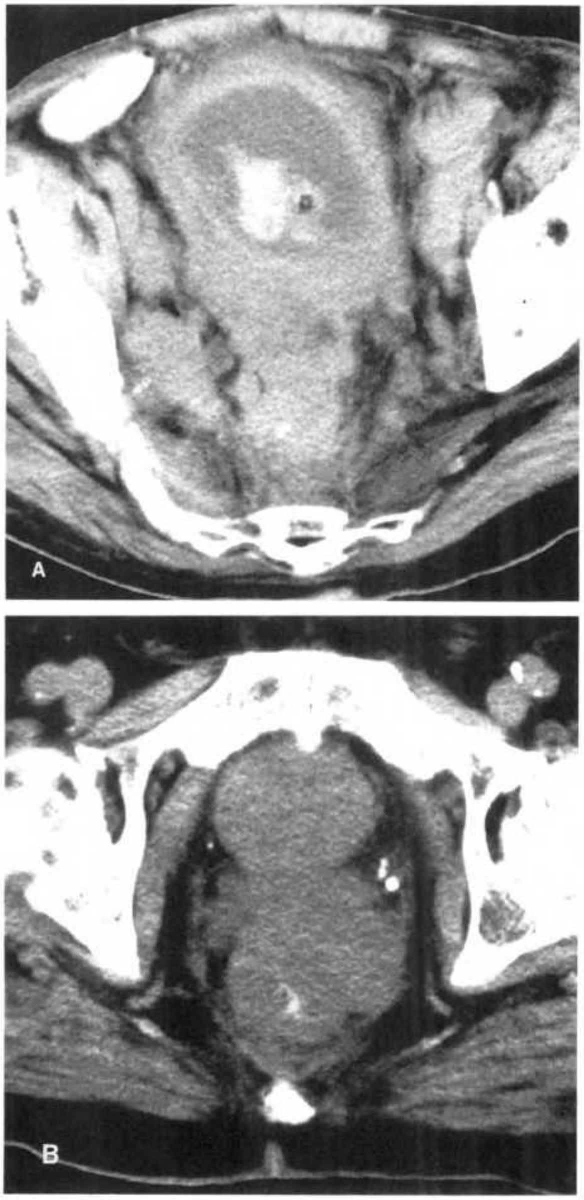


Fig. 2 CT scan appearances of the rectal lesions. (A) Type 1 rectal lesion (case 3). (B) Type 2 rectal lesion (case 4).

However, periodically during and at the end of the procedure, the resectoscope was removed from its sheath to allow drainage of the irrigant fluid and tumour chippings. Since very little of the irrigant solution drains back, only one 3-litre bag of irrigant solution was used for each resection. Two patients also underwent channel transurethral resections of their malignant prostates under the same anaesthesia.

Results

The results of treatment are shown in Table 2. The TARP procedure is simple to perform, taking approximately 15 min, and was repeated for recurrent symptomatic disease in 2 patients. All 5 patients have since died. In 2 cases the procedure was repeated for recurrent disease and obstructive symptoms and both patients survived for 27 weeks following their initial surgery. The average symptom-free survival was approximately 16 weeks.

Complications such as post-operative haemorrhage and irrigation fluid absorption were not encountered. Serum electrolytes were checked post-operatively and hyponatraemia did not occur. In one patient the operation was complicated by rectal perforation, which became clinically apparent within 8 h of surgery. An emergency laparotomy was carried out and a sigmoid end colostomy was fashioned. This patient died 3 weeks later from a massive pulmonary embolus, despite prophylactic heparinisation. Two deaths were due to renal failure secondary to malignant ureteric obstruction and another patient died following a major stroke. The cause of death in the fifth patient remains uncertain, since a post mortem was not performed.

Discussion

We have used the technique of transanal prostatic resection as a palliative procedure for patients with locally advanced hormone resistant disease causing symptomatic rectal obstruction. Although irradiation to the malignant prostate may provide adequate palliation (Green, 1974; Siegel *et al.*, 1986), this was not true in the case of the single patient who received this treatment. Furthermore, because of the initial tissue necrosis and oedema resulting from radiotherapy, we feel that this form of treatment might worsen the obstruction and the only alternative for these patients would be a defunctioning colostomy.

All but one patient had excellent palliation until the time of death. Sosa and Pitts (1988) obtained adequate palliation by transanal resection of rectal and pararectal tumours in 20 of 23 resections. Ottery *et al.* (1986) performed 6 endoscopic resections in one patient for local control of a rectal tumour.

In all 5 patients the obstruction was well above the level of the anal sphincter. Although Fry *et al.* (1979) described a low annular malignant prostatic stricture involving the anal sphincter, we would not recommend TARP in this situation because of the

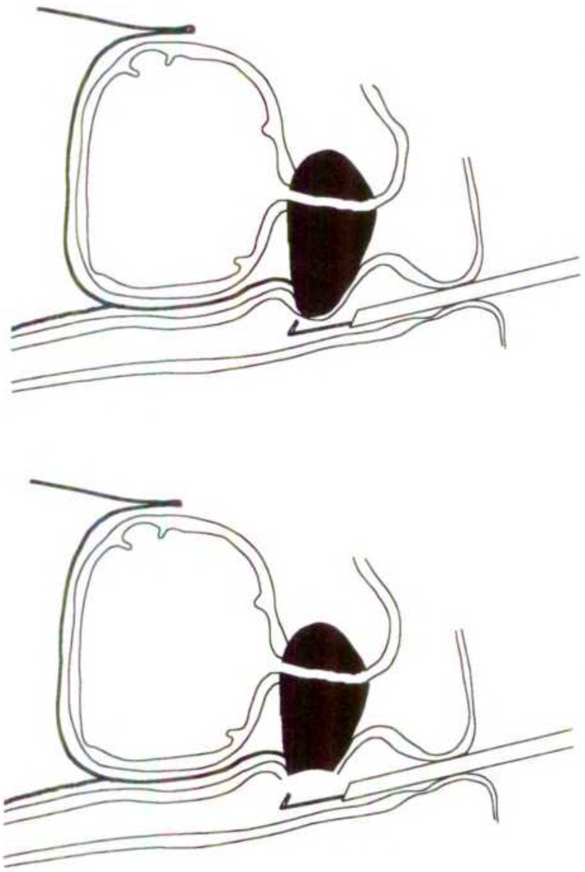


Fig. 3 Resection of a type 1 rectal lesion.

likelihood of rendering these patients faecally incontinent.

The complications in this small series were acceptable. Significant post-operative haemorrhage and post-operative fever were not encountered. Prophylactic parenteral antibiotics were administered to all patients at the time of anaesthetic induction and continued for 24 h. However, one case of rectal perforation was seen. Sosa and Pitts (1988) also reported one rectal perforation requiring laparotomy and colostomy in their 23 resections for rectal tumours. Although a major complication of this procedure, the formation of a colostomy would have been the alternative treatment for the original disease. Finally, absorption of the glycine irrigation fluid is a potential complication of transanal resection. Ottery *et al.* (1986) found no electrolyte abnormalities following 50 endoscopic transanal resections performed on 23 patients for rectal tumours; our findings were similar. We feel it is important to limit the operating time and the amount of irrigant used in order to minimise this risk.

Fry *et al.* (1979) reported ureteric obstruction in all 13 patients with symptomatic rectal obstruction secondary to rectal carcinoma. It is interesting that in 2 of our patients, locally advanced disease caused death secondary to uraemia with no evidence of body metastases. This may reflect the behaviour of the tumour in these cases where local invasion is a prominent feature.

In conclusion, TARP is a quick and easy procedure to perform for a competent resectionist and it can be repeated if necessary. It requires care to minimise the occurrence of rectal perforation. Antibiotic prophylaxis should be given to all patients and limiting the resection time to only one 2-litre bag of irrigant solution should reduce the dangers of fluid absorption. We recommend this procedure as an alternative to colostomy in the palliative treatment of patients with symptoms of rectal obstruction secondary to a hormone resistant malignant prostate.

Table 2 Results of TARP

Patient no.	*No. of transanal resections*	*Operation*	*Concurrent TURP*	*Post-operative pyrexia*	*Complications*	*Survival time (weeks)*	*Cause of death*
1	1	1	Yes	No	Nil	9	Unknown
2	1	1	No	Yes	Rectal perforation	3	Pulmonary embolism secondary to deep vein thrombosis
3	1	1	No	No	Nil	12	Cardiovascular accident
4	2	1	Yes	No	Nil	18	—
		2	No	No	Nil	9	Uraemia
5	2	1	No	No	Nil	23	—
		2	No	No	Nil	4	Uraemia

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The Treatment of Peyronie's Disease with Tamoxifen

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Summary—This is a preliminary study of the treatment of 36 patients with Peyronie's disease who received tamoxifen 20 mg twice daily for 3 months.

An improvement occurred in 16 of 20 patients with penile pain, in 11 of 31 patients with an erectile deformity and 12 of 35 patients had a plaque shrinkage of at least 1 cm. Some improvement occurred in 6 of the 8 patients with a histologically confirmed inflammatory infiltrate of the plaque but not in any of the 4 patients without an infiltrate. The inflammatory infiltrate was found in patients in whom the duration of the disease was less than 4 months.

The aetiology of Peyronie's disease remains a mystery and this has resulted in limited success from the various treatments that have been used (Chilton *et al.*, 1982). In the early stages of the disease there is an inflammatory infiltration within the subtunical layer, predominantly of T lymphocytes and macrophages (Fig. 1), leading to activation of the cytokine network and resultant fibrogenesis. The cytokine transforming growth factor-beta (TGF-b), released from platelets and activated macrophages, has been shown to be central in regulating inflammation, immune responses and tissue repair (Wahl *et al.*, 1989). A high concentration of TGF-b in the cellular environment causes macrophage deactivation and T lymphocyte suppression, thus decreasing the inflammatory response and reducing fibrogenesis.

Tamoxifen has been shown to increase the secretion of TGF-b from human fibroblasts *in vitro* and it should therefore inhibit the inflammatory response *in vivo* (Colletta *et al.*, 1990) (Fig. 2). Tamoxifen has been shown to have a beneficial effect in the treatment of the desmoid tumour, a condition which is histologically similar to Peyronie's disease. It was for these reasons that this preliminary study of tamoxifen in the treatment of Peyronie's disease was performed.

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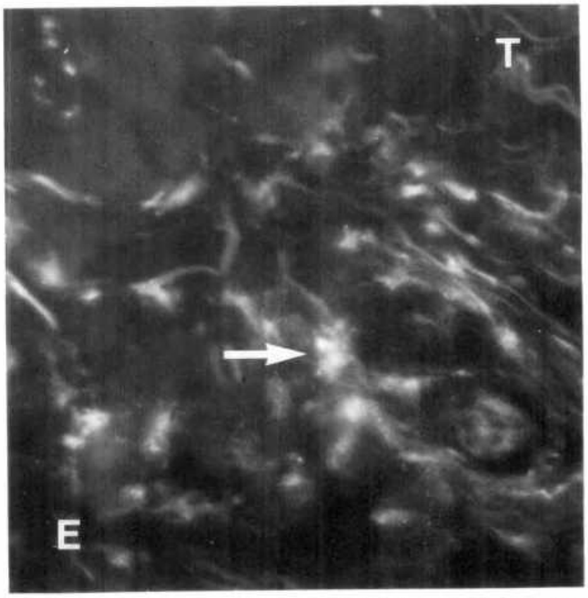

Fig. 1 Macrophages, demonstrated by the bright immunofluorescent stain (arrow), infiltrating within the subtunical space. T = tunica. E = erectile tissue.

Patients and Methods

Thirty-six patients with newly diagnosed Peyronie's disease were given tamoxifen 20 mg *bd* for 3 months. Their mean age was 51 years (range 27–68) and the mean duration of disease at presentation was 8 months (range 2–24). An assessment of the

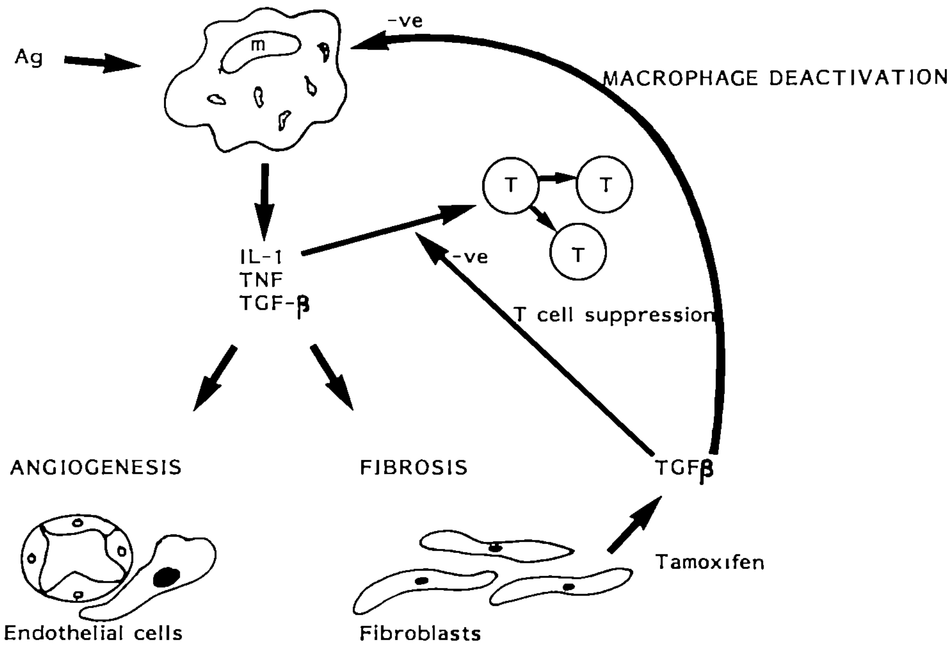

Fig. 2 Proposed mode of action of tamoxifen.

level of pain, the deformity angle on erection and the plaque size was performed at presentation and at 6-weekly intervals for 3 months. The pain level was scored as absent = 0, moderate = 1 and severe = 2, as in previous studies of the treatment of Peyronie's disease (Morgan and Pryor, 1978; Pryor and Farrell, 1983). Each patient assessed the angle of deformity to within 10 degrees as this was found to compare well with the deformity seen after an intracavernosal injection of a vasoactive agent (Ralph *et al.*, 1992). Plaque size was measured with a ruler to the nearest millimetre in the flaccid penis. An improvement was considered if there was a decreased pain score, a decrease in the deformity angle >10° and plaque shrinkage >1 cm.

A 1-mm biopsy of the plaque was taken under local anaesthesia from 12 patients with painful Peyronie's disease. The tissue was snap frozen to −70°C and 4-μm sections were prepared using a cryostat. Using direct immunofluorescence, the sections were then screened with a panel of monoclonal antibodies to assess the degree of cellular infiltration (Miller *et al.*, 1991). The response rate in those with an active infiltration was then observed.

Results

The results of the symptomatic improvement are shown in the Table. Penile pain improved in 16 (80%) of 20 patients, deformity in 11 (35%) of 31 patients with a deformity and plaque shrinkage occurred in 12 (34%) of 35 patients. There was some improvement in 20 of the 36 patients (55%) and no deterioration (Fig. 3).

Patients with early disease (duration <4 months) responded better than patients with a longer history and this was significantly so for a plaque shrinkage >1 cm ($P = 0.04$) (Figs 4–6).

Biopsy revealed an inflammatory infiltrate in 8 of the 12 patients with painful Peyronie's disease. The infiltrate consisted predominantly of activated macrophages and T lymphocytes (Fig. 1). An improvement occurred in 6 of these 8 patients,

Table Results

		Pre-treatment symptoms	*Post-treatment improvement*	
		No.	*No.*	*%*
Painful erection (score)	0	16	—	—
	1	11	8	73
	2	9	8	89
Deformity (degrees)	0	5	—	—
	<30	16	5	31
	>30	15	6	40
Plaque		35	12	34

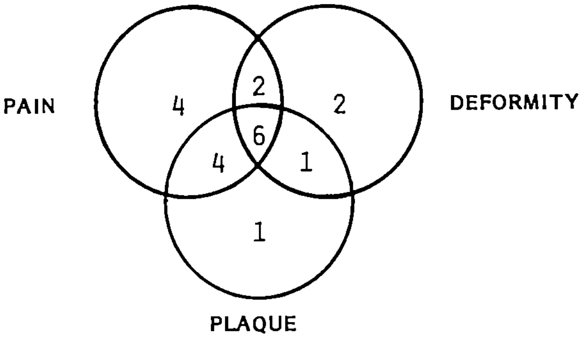

Fig. 3 Improvement in 1 or more symptoms in 20 patients.

consisting of pain resolution and plaque shrinkage in all and improved deformity in 4 patients. Patients without an inflammatory infiltration did not respond to treatment.

Two patients noticed a significant improvement in their Dupuytren's contracture whilst on treatment.

Cessation of treatment did not result in recurrence of pain or deformity in the short term and no patient has had a flare-up of the disease at a different site. Tamoxifen was well tolerated in all patients, but minor side effects were noticed in 5: reduced libido (3), facial flushing (2) and a reduced ejaculate volume (1).

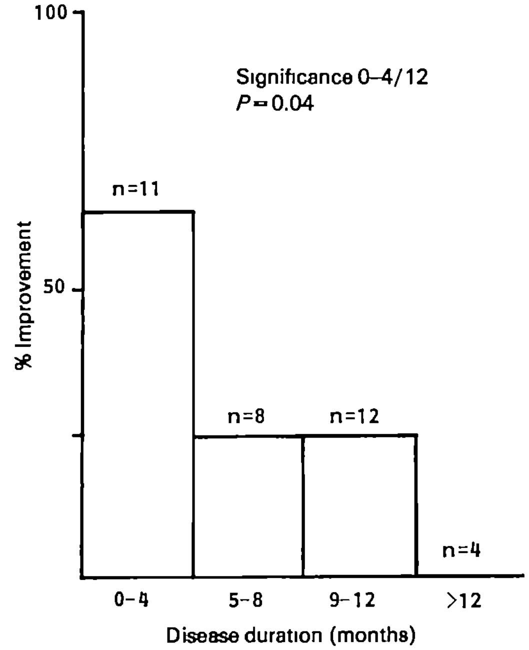

Fig. 5 Relationship between shrinkage of plaque and duration of disease.

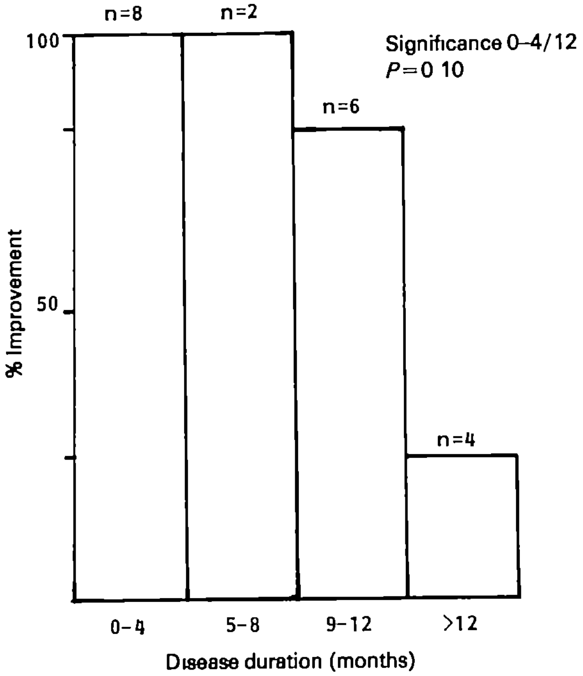

Fig. 4 Relationship between improvement in pain and duration of disease.

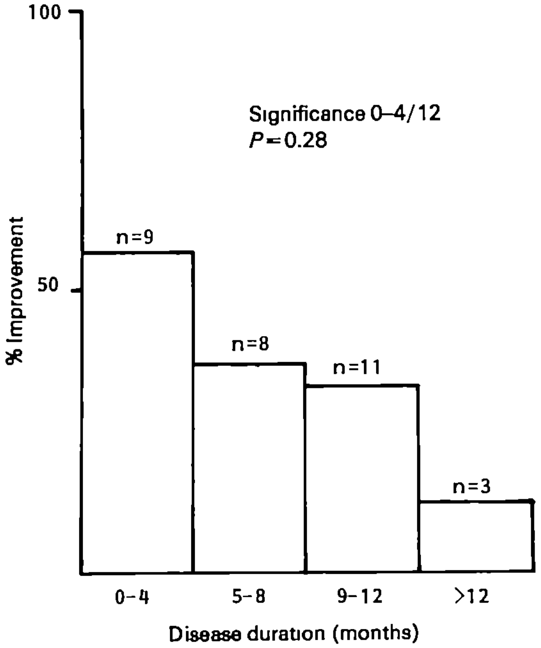

Fig. 6 Relationship between improvement in deformity and duration of disease.

Although all patients completed the 3-month course, the maximum effect was usually obtained after 6 weeks' therapy.

Discussion

The medical management of Peyronie's disease has generally been unsuccessful, with many agents having been tried. The current drug of choice is vitamin E, which can be expected to improve penile pain in 35% of patients but has minimal benefit in improving deformity or plaque size (Pryor and Farrell, 1983).

With the new knowledge of the cellular activity that occurs in the acute stage of Peyronie's disease, drugs acting at the molecular level can now be studied (Ralph *et al.*, unpublished data). The cytokine TGF-b, released by platelets and activated macrophages, appears to play a central role in the inflammatory response and wound healing. In normal healing it promotes matrix synthesis by fibroblasts and is self-regulated in an autocrine manner. However, higher concentrations of TGF-b in the cellular environment inhibit the inflammatory response, causing macrophage deactivation and T lymphocyte suppression, thus preventing further fibrogenesis (Wahl *et al.*, 1989). As tamoxifen increases TGF-b release from fibroblasts *in vitro*, its effect *in vivo* should be anti-inflammatory, with inhibition of fibrogenesis (Colletta *et al.*, 1990). The maximum benefit would therefore be expected in the early inflammatory stage of Peyronie's disease.

The response to treatment was evaluated by the patient's estimate of pain and deformity and the doctor's assessment of plaque size in the flaccid state. Consideration was given to the assessment of deformity by autophotography (Kelami, 1983), but the angle of deformity varies with the camera angle to the penis, as is apparent in video recordings of operations to correct a penile deformity. This may be overcome by using a defined camera angle: 90° to the maximum angle of deformity, but this requires the injection of a vasoactive agent. There is little justification for this as the patient's estimate of the deformity was found to correlate with the deformity found on inducing an erection (Ralph *et al.*, 1992). Furthermore, there is an incidence of penile fibrosis even following a single injection of papaverine (Pryor, 1987).

The overall response rate in this study was 55%, with 80% of patients reporting an improvement in pain, 35% an improvement in deformity and 34% experiencing plaque shrinkage. As expected, the greatest response occurred in patients with early disease (<4 months' duration). In this group the pain improved in 100%, the deformity in 56% and the plaque in 64%. Patients with a proven infiltrate on biopsy usually improved, whereas those without an infiltrate did not. This adds weight to the fact that tamoxifen may be acting in the proposed anti-inflammatory manner. It is desirable to carry out a controlled trial but the use of tamoxifen for this purpose has met with difficulties.

The natural history of Peyronie's disease is of an improvement, but the rate of remission in this study is greater than that occurring over a longer period in earlier studies. The condition may, however, worsen without treatment and so the results obtained from this study appear to be encouraging. A response to tamoxifen should be expected (1) within 6 weeks of treatment, (2) in early disease (<4 months) and (3) if the plaque is painful and soft.

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A New Vacuum Device as Alternative Treatment for Impotence

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Summary—Vacuum erection devices are an acceptable alternative for the management of erectile dysfunction. The safety of such devices has been questioned because of their effects on penile blood flow. We report the use of Doppler ultrasonography to assess arterial flow and its value in ensuring long-term safety of a new external vacuum device. Sixteen patients were studied. At 3 months it was possible to confirm the efficacy and safety of the method and model in 14 patients, 12 of whom had a significant improvement in their sexual function. By 10 months, only 6 were continuing to use the device. Doppler sonography appears to be an effective technique for assessing penile blood flow during restriction from a vacuum device. The new vacuum device provides a satisfactory short-term alternative to other more invasive forms of therapy.

It is now widely accepted that penile erection results from increased arterial inflow and decreased venous outflow (Lue and Tanagho, 1987). When artificially induced, these events are sufficient to produce an erection (Lue *et al.*, 1983). An erection can be obtained by placing the penis in a vacuum chamber to increase blood inflow and then reducing blood outflow by means of a constricting ring at the base of the penis. The constriction allows an increase of the intracavernous pressure above arterial pressure (Diederichs *et al.*, 1989). A number of studies have reported success and patient satisfaction using a vacuum device to manage impotence (Nadig *et al.*, 1986; Witherington, 1989; Sidi *et al.*, 1990; Turner *et al.*, 1990; Broderick *et al.*, 1991). Such therapy is associated with the development of ecchymoses or petechiae which usually disappear without treatment. In addition, the development of penile skin necrosis in a paraplegic patient has been reported (Meinhardt *et al.*, 1990). The development of such complications has restricted the use of vacuum therapy in the treatment of impotence.

There have been few studies on the effects of restriction of penile blood flow. Marmar *et al.* (1988) used plethysmography but this technique measures global pulse volume changes rather than blood flow. Katz *et al.* (1990) used a xenon washout technique, which provides an estimation of venous outflow and cannot be used in routine practice.

We have studied a newly designed vacuum device (PM Force Médicale, France). The original features are an easily removable constricting ring available in 3 sizes and 3 different diameters of rubber band to provide the most beneficial seal around the base of the penis during production of the vacuum. Doppler ultrasonography was used to check arterial flow during constriction and enabled the most appropriate rubber band and constricting ring to be selected. The acceptability and convenience of the device are also reported.

Patients and Methods

The study group comprised 16 men aged 30 to 70 years (average 51). A medical and sexual history was obtained and all patients underwent a physical examination, Doppler sonography of the penile arteries and nocturnal rigidimetry. These results were suggestive of an organic aetiology in all patients. They were offered the vacuum method of therapy. All gave their written consent and agreed to adhere to a 3-month follow-up.

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The device consists of a plastic cylinder attached by tubing to a separate hand pump (Fig. 1). It also includes a rubber band and constricting ring, both of which are available in 3 sizes (Fig. 2). All sizes of the constricting rings and rubber rings were tested. The patients were given full instructions on the use of the device. Doppler ultrasonography was carried out at this initial visit. Selection of the most appropriate constricting ring and rubber band was based on obtaining an erection-like state and continuous penile arterial flow with a constricting band in place. If the constricting band inhibited arterial inflow, a larger diameter band was used. Patients were assessed weekly for 3 months. Those who reported difficulty in using the device received further instruction. At the end of follow-up patients were questioned with regard to any difficulties they had encountered, their acceptance of the device and their satisfaction with the treatment. Data on sexual desire, quality and duration of penile rigidity before and after treatment were also collected.

Results

The use of Doppler ultrasonography during the initial demonstration of the device allowed us to choose the most adequate constricting ring size which did not inhibit arterial flow. Six patients used ring A (7 cm), 2 patients ring B (7.5 cm) and 8 ring C (8 cm). Fourteen of the 16 patients completed the initial period of study. One changed to an alternative therapy and the other underwent a surgical operation unrelated to impotence. The average use of the device was 4 times a week. Twelve of the 14 men obtained erections allowing vaginal penetration and intercourse. Two obtained tumescence but insufficient rigidity for penetration. One patient reported mild, transient skin petechiae. The improvements in sexual function are shown in Table 1 and the acceptability of the device in Table 2.

The 2 patients who expressed dissatisfaction were those who were unable to achieve an erection satisfactory for penetration. Six patients reported on the benefits of the easily removable constricting ring. However, 2 found it embarrassing and one did not use it on occasions. Six patients reported recovery of an occasional early morning erection. The device has now been in use for 10 months and 6 continue to use it with a mean follow-up of 24 ± 9 weeks. Six patients are now receiving injectable pharmacotherapy and 2 psychotherapy.

Discussion

We have confirmed the results of other authors that the use of an external vacuum device is a safe and

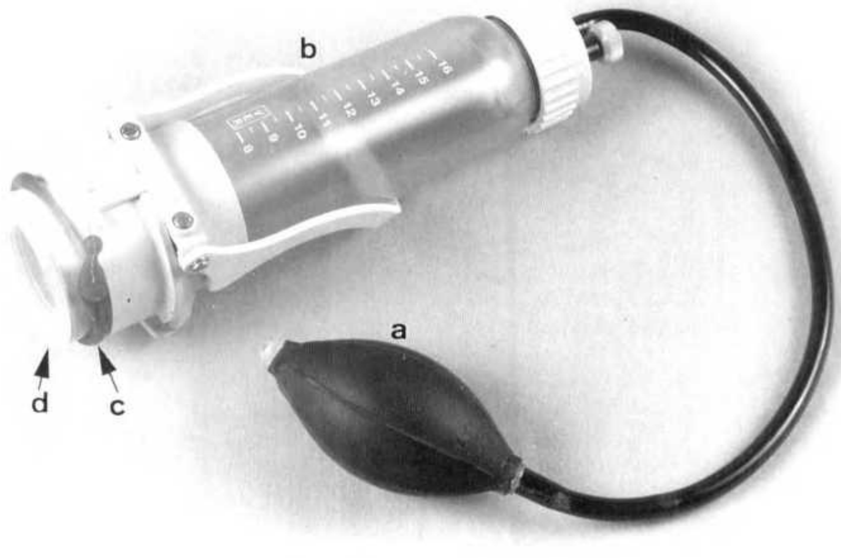

Fig. 1 The vacuum device. a: hand pump. b: plastic cylinder. c: constricting ring. d: rubber band.

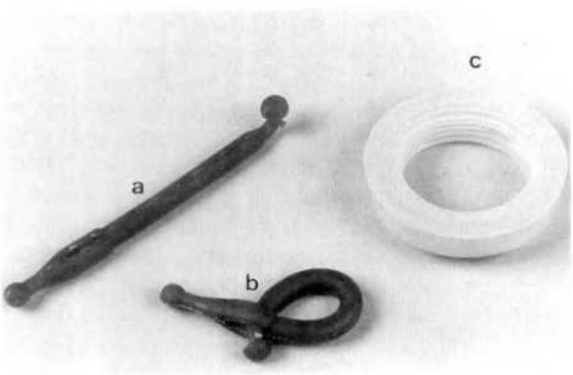

Fig. 2 Optional size pieces. a: constricting ring opened. b: constricting ring closed. c: rubber band.

Table 1 Satisfaction with the Vacuum Device over a 3-month Treatment Period

	*Median score**		
	Before treatment	*After treatment*	*P†*
Sexual desire	5	7	<0.01
Sexual satisfaction	4	6	<0.01
Duration of erection	5	7	<0.01
Penile rigidity	4	6	<0.01

*Score range 0–10.
†Wilcoxon Signed Rank Test.

Table 2 Acceptability of the Device by 14 Impotent Men after 3 Months' use

Question	*Yes*	*No*
Did you accept the method?	14	0
Did you find the device easy to use?	14	0
Did you feel any pain using the device?	1	13
Did you have any ejaculation problems during constriction?	0	12
Did you recover early morning erections*	6	6
Were you satisfied with the device?	12	2
Did your partner accept the device?†	10	0

*Two patients used to have early morning erections before the study.
†Two partners did not answer this question.

satisfactory treatment of erectile dysfunction (Nadig *et al.*, 1986; Witherington, 1989; Sidi *et al.*, 1990; Broderick *et al.*, 1991). There has been a significant improvement in sexual function in 12 of the 14 men who used the device for 3 months. In most cases this improvement included recovery of sexual desire, better penile rigidity and a longer duration of erection, as well as improved sexual satisfaction. Six patients reported recovery of occasional early morning erections, an important physiological and psychological event.

In contrast to previous studies (Nadig *et al.*, 1986; Sidi *et al.*, 1990; Turner *et al.*, 1990), the improvement in sexual function in our patients may be attributed to several factors. The adaptable rubber band system proved highly effective in maintaining the vacuum during development of the erection. The use of Doppler ultrasound in determining the most appropriate size of constriction ring avoided the side effects reported by Nadig *et al.* (1986) and Meinhard *et al.* (1990). Only 1 patient developed minor and transient petechiae on one occasion and this did not hinder further use of the device. One patient developed mild pain which resolved with the use of a lower vacuum pressure. In contrast to a previous report (Witherington, 1989), none of our patients complained of pain on ejaculation as the restricting ring allowed instantaneous removal.

Doppler measurements were made proximal and distal to the constricting ring. No significant difference between the 2 Doppler signals was found and we therefore limited our studies to the presence of penile arterial flow. Our observations may explain the results of a previous study by Broderick *et al.* (1990), who used magnetic resonance imaging and reported that congestion of the corpora cavernosa during constriction was accompanied by a relatively lower signal intensity in the central arteries. This probably results from an increase in penile blood velocity during constriction rather than an increase in arterial flow.

Vacuum devices are useful alternatives in the treatment of impotence. A careful check of arterial circulation during constriction with Doppler sonography improves the safety and efficacy of these devices.

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Testicular Cancer and Cryptorchidism

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Summary—The records of 273 patients with germ cell tumours of the testis referred between 1970 and July 1991 were reviewed. There were 25 (9%) black, 40 (14%) mixed race and 214 (77%) white patients. Histology showed seminoma in 53% and non-seminomatous and germ cell tumours in 47% of patients. Maldescent of the testis (MDT) was found in 30 patients—an incidence of 11% overall. MDT was present in 8 of 25 (32%) black, 7 of 40 (18%) mixed race and 15 of 214 (7%) white patients with testicular cancer. The incidence of MDT was statistically significantly higher in both black and mixed race patients compared with white patients. None of the black patients had undergone orchiopexy but 71% of mixed race and 87% of white patients had done so. This resulted in a different pattern of presentation in black compared with mixed race and white patients with MDT and testicular cancer. The mean age was 40 years for black, 32 years for mixed race and 33 years for white patients. Black patients presented with abdominal or inguinal tumours rather than scrotal tumours and they had an increased tendency to present with seminomas.

Testicular cancer is associated with maldescent of the testis in 4 to 11% of cases (Waterhouse, 1965; Chilvers and Pike, 1989; Forman, 1990). Its incidence is also affected by race—it usually occurs in white patients and is rare in black and almost all non-Caucasion populations (Daniels *et al.*, 1981; Forman, 1990). The highest incidence is in Denmark, at 4.9/100,000 annually, and lowest in Nigeria, at 0.1/100,000 annually (Daniels *et al.*, 1981). A survey of black patients in Johannesburg in the 1950s showed an incidence of 0.2/100,000 annually (Oettle, 1964).

A review at Groote Schuur Hospital (GSH) of the results of therapy in patients with seminoma showed a high incidence of maldescent in the few black patients seen (Abratt *et al.*, 1987a). This finding prompted a review of patients with testicular cancer and MDT seen at Urology-Radiotherapy clinics at GSH and 2 allied hospitals.

Patients and Methods

The records of all 273 patients with germ cell tumours of the testis referred to Urology-Radiotherapy clinics at GSH, Frere Hospital in East London and Provincial Hospital in Port Elizabeth between 1970 and July 1991 were reviewed. Essentially all patients with testicular cancer in the areas served by these hospitals are referred to these clinics.

MDT was found in 30 patients. The staging system used was similar to that used for scrotal tumours: stage 1 is localised disease, stage 2 is retroperitoneal lymph node involvement, which may be non-bulky (non-palpable or <5 cm in diameter) or bulky (palpable or >5 cm in diameter), and stage 3 for more extensive disease.

Statistically significant differences were evaluated with Fisher's exact test.

Results

Patients with testicular cancer

The 273 patients with germ cell tumours of the testis consisted of 173 (62%) from GSH, 65 (23%) from Port Elizabeth and 41 (15%) from East London. The mean age was 34 years for all patients, 39 years for those with seminomas and 30 years for those with non-seminomatous germ cell tumours (NSGCT). There were 25 (9%) black, 40 (14%)

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mixed race patients and 214 (77%) white patients. Histological examination revealed seminoma in 53% and NSGCT in 47% of patients.

MDT was found in 30 patients, with an incidence of 11% overall. MDT was present in 8 of 25 (32%) black, 7 of 40 (18%) mixed race and 15 of 214 (7%) white patients with testicular cancer. The incidence of MDT was statistically significantly higher in both black ($P=0.0004$) and mixed race patients ($P=0.02$) compared with white patients.

Patients with testicular cancer and MDT

In patients with MDT, the mean age was 34 years (range 16–52) overall, 40 years (30–52) for the black, 32 years (28–35) for mixed race and 33 years (16–47) for white patients. The side of the MDT is shown in Table 1. The testes were bilaterally undescended in 23% of cases and this was independent of race.

The median age at the time of orchiopexy in those who underwent the operation was 8 years (range 5–20). None of the black patients had undergone orchiopexy (Table 1) but 71% of the mixed race and 87% of the white patients had done so. The lower incidence of orchiopexy in black compared with mixed race ($P=0.007$) and white patients ($P=0.0001$) was statistically significantly different.

The testicular tumours in these patients were situated on the right in 14 (47%) and the left in 16 (53%). The tumours were in an undescended testis in 29 patients and in the contralateral normally descended testis in 1 patient. The site of the tumour (abdomen, inguinal or scrotum) and the histology (seminoma or NSGCT) are shown in Table 2. The abdominal tumours were all located in the pelvis or iliac fossa.

The relationship of histology to race group is shown in Table 2. There were 20 (67%) seminomas and 10 (33%) NSGCT. There was a tendency to a higher proportion of seminomas in black (88%) compared with mixed race and white patients (59%). Of the patients with NSGCT, 5 had embryonal carcinoma, 4 had teratocarcinoma and 4 had pure choriocarcinoma.

Table 1 Side of MDT and Proportion of Patients who Underwent Orchiopexy

	Black (%)	*Mixed race (%)*	*White (%)*	*All (%)*
Side of MDT				
Right	3 (38)	2 (29)	7 (47)	12 (40)
Left	3 (38)	3 (43)	5 (35)	11 (37)
Bilateral	2 (25)	2 (29)	3 (20)	7 (23)
Total	8 (100)	7 (100)	15 (100)	30 (100)
Corrected by orchiopexy				
No	8 (100)	2 (29)	2 (13)	12 (40)
Yes	0 (–)	5 (71)	13 (87)	18 (60)

Table 2 Testicular Tumours in Patients with Undescended Testis

	Black (%)	*Mixed race (%)*	*White (%)*	*All (%)*
Site of tumour				
Abdomen	6 (75)	1 (14)	1 (7)	8 (27)
Inguinal	2 (25)	1 (14)	1 (7)	4 (13)
Scrotum	0 (0)	5 (71)	13 (87)	18 (60)
Histology				
Seminoma	7 (88)	4 (57)	9 (60)	20 (67)
NSGCT	1 (13)	3 (43)	6 (40)	10 (33)

The relationship of histology to the site of tumour is shown in Table 3. The incidence of seminoma was higher at 92% in patients with abdominal or inguinal tumours compared with 50% in those with scrotal tumours ($P=0.02$).

The stage of disease and its relationship to histology and site are shown in Table 4. There was a greater tendency for patients with seminoma to present with stage 1 disease (55%) compared with those with NSGCT (30%). Although patients with abdominal disease can be expected to present late, 3 of 8 (38%) presented with localised (stage 1) disease.

Treatment and outcome

The overall 5-year survival rate (life table) for the patients with seminoma was 76%, with 1 patient dying of disease after 5 years' follow-up. Of the patients with seminoma, 15 are alive with no evidence of disease. This includes 11 patients with stage 1 and 2 (non-bulky) disease: 8 of these had an inguinal orchiectomy and 3 patients had an abdominal orchiectomy. All of these patients received retroperitoneal irradiation. An additional 4 patients are free of disease after having cisplatin combination chemotherapy; 1 of these had presented with inoperable bulky inguinal disease without metastases (Abratt *et al.*, 1987b), 2 patients had bulky stage 2 disease and 1 had stage 3 disease.

Table 3 Relationship of Histology to Site of Tumours (%)

	Abdominal	*Inguinal*	*Scrotal*
Seminoma	7 (88)	4 (100)	9 (50)
NSGCT	1 (13)	0	9 (50)

Table 4 Stage, Histology and Site of Tumour

	Histology		*Site*			
Stage	*Seminoma (%)*	*NSGCT (%)*	*Abdomen (%)*	*Inguinal (%)*	*Scrotal (%)*	*All (%)*
1	11 (55)	3 (30)	3 (38)	2 (50)	9 (50)	14 (46)
2 Non-bulky	2 (10)	2 (20)	0	1 (25)	2 (12)	4 (13)
2 Bulky	2 (10)	1 (10)	1 (13)	0	3 (17)	3 (10)
3	5 (25)	4 (40)	4 (50)	1 (25)	4 (22)	9 (30)

Five patients with seminoma died of disease. These included 2 with stage 3 disease who were treated before the availability of cisplatin combination chemotherapy and 1 with stage 3 disease who refused therapy. Another 2 patients, 1 with bulky stage 2 and 1 with advanced stage 3 disease died despite cisplatin combination chemotherapy.

The overall 5-year survival rate (life table) for the patients with NSGCT was 51%. Of the 10 patients with NSGCT, 6 are alive and free of disease. Four of those patients had stage 1 and stage 2 non-bulky disease and were treated by orchiectomy followed in 2 patients by lymphadenectomy. An additional 2 patients with stage 3 tumours are alive and free of disease after cisplatin combination chemotherapy.

Four patients with NSCGT have died. Of these, 2 patients were treated before the availability of cisplatin, 1 of these had stage 2 non-bulky disease and relapsed after lymph node dissection and 1 had stage 2 bulky disease. The other 2 patients, 1 with bulky stage 2 and one with stage 3 disease, died despite cisplatin combination chemotherapy.

Discussion

Testicular cancer is rare in black and mixed race patients. In this review, the incidence of MDT was higher at 32% in black patients compared with 18% in mixed race and 7% in white patients.

Testicular cancer is caused by both genetic and non-genetic factors. The influence of genetic factors is indicated by the different incidences in racial groups, the many reports of familial testicular cancer, the association between testicular cancer and specific HLA types as well as non-random chromsome abnormalities (Forman, 1990).

The aetiological mechanism of the link between MDT and testicular cancer is unclear. The incidence of MDT (11%) in familial cases of testicular cancer is the same as in non-familial ones, which indicates that genetic factors are independent of MDT (Dieckmann *et al.*, 1987). It is thought most likely that both MDT and testicular cancer have a common cause, such as an abnormal endocrinological environment (Forman, 1990). It is unlikely that the abnormal location of the testis outside the scrotum, with consequent exposure to factors such as high temperature, is causative. Orchiopexy is not protective and there is an increased incidence of cancer in the contralateral testis in patients with unilateral MDT (Forman, 1990).

The high incidence of MDT indicates a decrease in other aetiological factors in the black and, to a lesser extent, in the mixed race patients with testicular cancer.

In the patients with testicular cancer and MDT, the mean age of 34 years at presentation is similar to that seen in patients without MDT, as reported by Batata *et al.* (1982). The frequency of seminoma decreases with descent of the testis from the abdomen into the scrotum (Batata *et al.*, 1982; Halme *et al.*, 1989). Seminoma was present in 92% of patients with abdominal or inguinal tumours and in 50% of those with scrotal tumours.

Orchiopexy affects the pattern of clinical presentation. None of the black patients had orchiopexy compared with 71% of the mixed race and 87% of the white patients. All black patients with MDT therefore had abdominal or inguinal tumours and they had a higher proportion of seminomas (88% *versus* 59%). The latter resulted in black patients being older at presentation (40 years *versus* 33).

The prognosis in patients with testicular cancer and MDT is primarily affected by the initial stage and histological type (Batata *et al.*, 1982). The presence of localised seminoma in 3 of the 8 patients with abdominal disease, and their good prognosis after further treatment by orchiectomy and retroperitoneal irradiation, are notable.

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Instillation of Silver Nitrate in the Treatment of Chyluria

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Summary—A series of 62 patients with chyluria received instillations of 1% silver nitrate in the renal pelvis over an 8-year period; 51 patients responded well but 11 showed no response to treatment. Follow-up ranged from 2 to 7 years.

The treatment was found to be safe, effective and minimally invasive.

Chyluria occurs as a result of communication between the lymphatics and the renal pelvis and usually indicates a chronic stage of filarial disease (Ohyama *et al.*, 1979). Although not life-threatening, the disease can be debilitating. Chyluria is rare in the Western world but the incidence in Asian countries is fairly high (Tan *et al.*, 1990). In the last 8 years we have treated 62 patients with chyluria and have assessed the effectiveness of instillations of silver nitrate.

Patients and Methods

The study group included 38 males and 24 females, most of whom were in their second or third decade. The youngest patient was a 16-year-old girl and the oldest a 65-year-old man (Table 1). All patients presented with milky white urine, the duration of disease ranging from 6 months to 10 years; 23 patients had chyluria for more than 5 years. The associated symptoms are shown in Table 2.

The diagnosis was made by observation of the urine and confirmed by ether test. Special investigations included intravenous urography (IVU) in 39 patients, radioisotope renography in 16 and ultrasonography in 32. Patients with a structural or functional abnormality of the kidney (*e.g.* poor function, stone, hydronephrosis, medical disease) were excluded from the study. Lymphangiography was carried out in 7 cases.

Table 1 Age Distribution in 62 Patients

Age (years)	*No of patients*	*%*
<20	6	10
20–30	21	34
30–40	24	39
>40	11	18

Table 2 Associated Symptoms

Symptoms	*No. of patients*	*%*
Passage of chylous clots	33	53
Retention of urine due to clots	5	8
Haematochyluria	13	21
Flank pain	6	10
Frequency/dysuria	10	16
Weakness	12	19
Fever with rigors	3	5

All patients underwent cystoscopy (under local anaesthesia) after a fatty meal. The chylous efflux was observed to identify the affected side and bulb ureterography was performed. Chyluria was unilateral in 52 patients (84%) and bilateral in 10 (16%).

The instillations were performed under local anaesthesia. A ureteric catheter was passed up to the renal pelvis on the affected side and 10 ml of 1% silver nitrate were instilled every half hour for 2 h (4 times). This comprised 1 course. All patients received suitable antibiotic cover.

In patients with bilateral chyluria only one side was treated at a time, with an interval of 6 weeks between instillations.

A total of 41 patients received 1 course of treatment, 8 received 2 courses and 11 received 3

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courses. There was a gap of 6 weeks between courses. One patient had an ipsilateral recurrence of chyluria 4 months after hilar clearance surgery and he received 1 course of silver nitrate treatment.

All patients were followed up and urine was examined for chyluria. IVU was performed in 28 patients (45%), radioisotope renography in 22 (35%) and ultrasonography in 26 (42%). Follow-up ranged from 2 to 7 years.

Results

Of the 39 patients who had a pre-treatment IVU, pyelolymphatic communications were seen in only 8. Bulb ureterography, which was performed in all cases, revealed varying degrees of pyelolymphatic communication in 51. Only 7 patients underwent lymphangiography and in 4 cases it was inconclusive.

Sixty patients had clear urine after their first course of treatment and 2 showed no response. In 41 of these 60 patients the urine continued to remain clear during follow-up extending from 2 to 7 years. This was regarded as a permanent remission. Chyluria recurred in 19 patients; in 17 cases it developed within 1 year of treatment, in 1 it occurred 15 months and in the other 20 months after treatment. All 19 patients received a second course of instillations, after which 8 (42%) had a permanent remission. In the remaining 11 patients chyluria recurred within 1 year. All underwent a third course but only 2 had a permanent remission and in the remaining 9 cases recurrence was noted 4 to 7 months after treatment. Nine of these 11 patients had a severe degree of pyelolymphatic communication.

Two patients who did not respond to the first course received a total of 3 courses, again with no response. All patients who failed to respond to treatment were advised to undergo surgery.

One patient treated by hilar clearance elsewhere had not received silver nitrate instillations before operation. He developed a recurrence of disease on the same side and responded well to 1 course of treatment. One year later he remains symptom-free.

After instillation of silver nitrate many patients complained of flank pain, nausea, vomiting and occasionally haematuria. These symptoms varied in severity but all subsided in 24 to 48 h. Although the symptoms were subjective, it was noted that patients with severe symptoms were more likely to respond well to treatment.

IVU, radioisotope renography and ultrasonography carried out after treatment failed to show any structural or functional renal changes that might suggest renal damage.

Discussion

Chyluria can be classifed as parasitic or non-parasitic. In the former group filariasis remains the prime cause, although other parasites are occasionally responsible (Lloyd-Davis *et al.*, 1967). As observed by Tan *et al.* (1990), non-parasitic causes such as malignant tumours of the thoracic duct, pregnancy, trauma, *etc*, are rare and were not seen in this study. Parasitic infection causes obstruction to the retroperitoneal lymphatics, leading to dilatation, proliferation and subsequent rupture of the lymphatics into the pelvicaliceal system (Chang *et al.*, 1973). Although chyluria can occur anywhere in the urinary tract, chyluria of renal origin is most common (Akisada and Tani, 1968).

Chyluria, haematochyluria, the passage of chylous clots in the urine and dysuria are common modes of presentation (Yu *et al.*, 1978). Although the disease is not life-threatening, it can lead to considerable weakness and weight loss and persistent chyluria can cause abnormalities in the immune system (Date *et al.*, 1981).

The diagnosis of chyluria can be made simply by observing the urine sample. Lymphangiography is advocated to localise the pyelolymphatic communications (Yu *et al.*, 1978). We have found that bulb ureterography is useful not only to identify the affected side but also to assess the severity of the pyelolymphatic communications, which was one of the factors in predicting response to treatment with silver nitrate instillations. IVU was not helpful in delineating pyelolymphatic leaks.

Amongst the treatments recommended for chyluria are renal decapsulation (Torres and Estrada, 1962), lymphatic venous anastomosis (Cockett and Goodwin, 1962), hilar clearance of the lymphatics (Chang *et al.*, 1973; Yu *et al.*, 1978) and nephrectomy (Yamauchi, 1945). Non-operative treatment includes reduction of fat in the diet or a diet containing medium chain triglycerides (Hashim *et al.*, 1964) and the instillation of silver nitrate in the renal pelvis.

When instilled in the renal pelvis, silver nitrate induces an inflammatory reaction in the lymphatics. This causes chemical lymphangitis and oedema of the lymphatic channels, and the resultant blockage leads to immediate relief and subsequent healing by fibrosis resulting in permanent remission.

Tan *et al.* (1990) reported good results with 0.5%

silver nitrate. Okamoto and Ohi (1983) used 0.1% initially, with a gradual increase to 0.5%. They administered instillations 2 to 3 times a week 10 or more times. We always used 1% silver nitrate solutions. After treatment, most patients complained of flank pain, nausea, vomiting, *etc*, and in patients with bilateral disease we therefore treated one side at a time. Patients received a maximum of 3 courses. It was found that 42% of patients responded well to a second course but only 18% showed a good response to a third course.

An approximate prediction of response can be made by assessing the severity of the pyelolymphatic communication on bulb ureterography or according to the severity of symptoms following treatment. Neither duration of chyluria nor bilaterality of disease had any correlation with the response rate.

Of the 11 patients who failed to respond to treatment, 9 developed a recurrence within 1 year of treatment and 2 showed recurrence between 1 and 2 years after treatment. After 2 years' remission, no recurrence was found after a maximum follow-up of 7 years. It was concluded that the instillation of silver nitrate into the renal pelvis is a safe, minimally invasive and effective treatment for chyluria.

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Wilms' Tumour in New Zealand 1960–1986

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Summary—Between 1960 and 1986, 177 cases of Wilms' tumour were reported to the New Zealand National Cancer Registry. There was an equal sex distribution and 93.2% of patients were in the paediatric age group with a mean age of 3.4 years. The mean symptom interval was 2.0 months and the majority of patients presented with localised disease, although the incidence of advanced disease was greater than that reported from other series. The 5-year survival rate for all cases was 52.5%. Data were divided into patients presenting before and after the publication of the first National Wilms' Tumour Study (NWTS) in the United States in 1976. In patients presenting after 1976 the diagnosis was based on histology in 100%, compared to 58.6% in patients before 1977. Treatment was considered curative in a greater proportion of the post-1976 group. Treatment modalities reflected the recommendations of the NWTS and the 5-year survival rate of this group was 78.3%, this being similar to that reported from the NWTS. Multivariate analysis showed patient age, symptom interval, tumour stage and treatment (pre- and post-NWTS) to be independent predictors of survival.

Over the last 20 years there has been considerable activity directed towards the classification and management of Wilms' tumour (WT). In 1969 the National Wilms' Tumour Study Group (NWTS) was established and since that time numerous reports, emanating from the 3 studies initiated by the NWTS, have detailed advances in the understanding of the behaviour and in the management of WT (Belasco and D'Angio, 1981). Specifically, the treatment protocols developed by the NWTS have resulted in a dramatic improvement in the survival of patients with this form of malignancy (D'Angio *et al.*, 1989).

The NWTS collated data from institutions in the United States and since the publication of the initial NWTS few additional reports have evaluated the clinical features and survival of patients with WT who have been treated outside that country. This study was undertaken to record the clinical characteristics and survival data of patients presenting with WT in New Zealand between 1960 and 1986. The treatment and outcome of patients presenting prior to, and following, the publication of the first NWTS by D'Angio *et al.* (1976) were compared in order to evaluate the impact of the results of that study on the survival of patients treated in a non-collaborating centre.

Patients and Methods

The New Zealand Cancer Registry has operated since 1948 and has been population-based since 1960 (Foster, 1977). Malignant tumours identified in public and private hospital admissions are registered and coded according to the International Classification of Disease for Oncology (ICD) currently using the 9th edition. Registration details include patient's age, sex, occupation, race and symptom interval (from first sign or symptom until diagnosis). Stage and grade of tumour, and aim and type of treatment are also recorded. The results from post mortem examinations and information from death certificates are abstracted by the Registry. Cancer registrations are matched with death certificate data to provide basic survival information for patients dying in New Zealand.

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All registrations classified under ICD code 189.0 (malignant neoplasms of the kidney, excluding the renal pelvis) were retrieved for the period 1960-1986. A major expansion in the registration record occurred in 1960 and case ascertainment was complete to the end of 1986 at the time of the study. All patients diagnosed with WT were identified and the registration data were evaluated in an attempt to identify parameters of prognostic importance. The data were analysed using the Statistical Analysis System (SAS, 1988) and actuarial survival analysis was undertaken using the Kaplan-Meier method for right censored data (Kaplan and Meier, 1958). Univariate parameters were tested using the log rank test and multivariate analysis undertaken using a log-logistic model (Kalbfleisch and Prentice, 1982).

In New Zealand there were no established protocols for the management of WT before the publication of the NWTS. In 1977 the protocols of the NWTS were adopted nationally and remained in use beyond 1986, the last year of registrations in this present study. In the analysis the registrations were divided into those made prior to and following the publication of the first NWTS report to determine the impact of that report on the outcome of WT patients in New Zealand. For the purpose of this study the pre-NWTS group was taken as all registrations prior to 1977, while the post-NWTS group was taken as all registrations after 1976.

Results

Patient data

During the 27-year period selected for study, 177 patients with WT were notified to the New Zealand Cancer Registry. The mean annual registration rate was 6.6 patients and annual registrations ranged from 1 patient in 1969 to 12 patients in 1984. The majority of patients (93.2%) were in the paediatric age group (< 15 years), although 12 cases were seen in adults (Fig. 1). The age-standardised incidence rate for WT in the New Zealand paediatric population for the period of study was $6.8/10^6$ person-years. The rates for the 5-year periods commencing 1960, 1965, 1970, 1975 and 1980 were 6.22, 6.16, 5.97, 6.19 and $8.52/10^6$ person-years respectively. There was an equal sex distribution

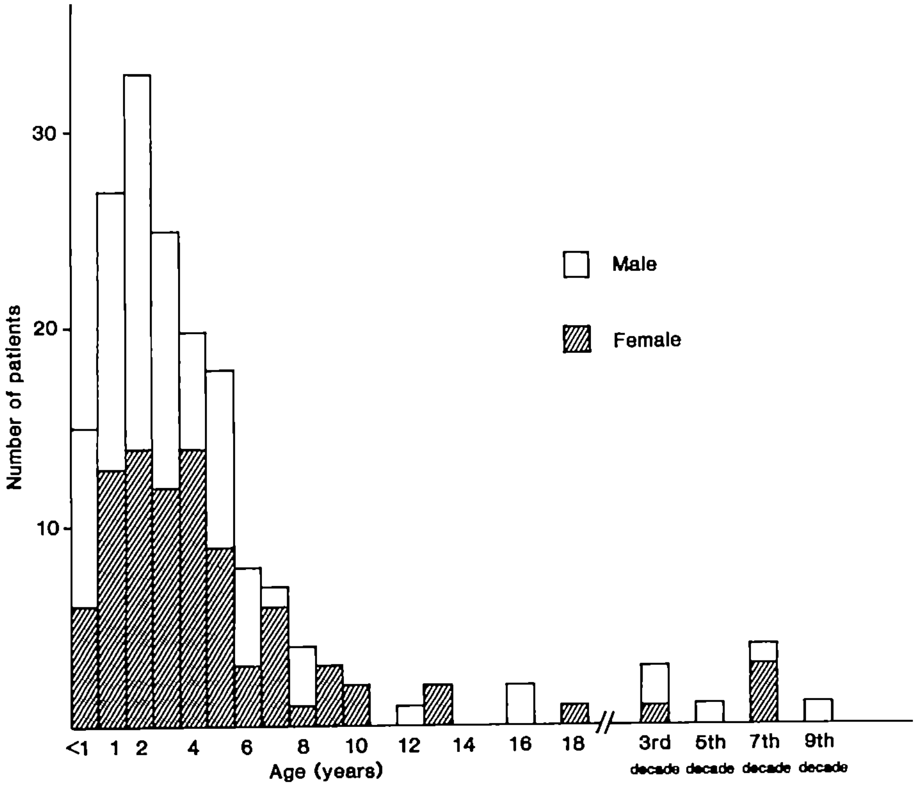

Fig. 1 Age and sex distribution of patients.

with 89 female and 87 male patients notified, the age-standardised incidence of WT in the male and female paediatric population being 6.4 and 7.2/10^6 person-years respectively.

Of the paediatric patients, the mean age at presentation was 3.4 years (females 3.8 years and males 2.9 years). The 12 adult patients ranged in age from 16 to 83 years (mean 42.4 years).

The indigenous people of New Zealand, the Maori, comprise 8% of the total population. The paediatric age-standardised incidence rate for WT in the Maori and non-Maori populations were 6.8 and 6.9/10^6 person-years respectively.

The mean symptom interval was 2.0 months and 40.7% of patients presented with a stated symptom interval of less than 1 month. The maximum time to presentation was 17 months.

Clinical examination was the only diagnostic criterion in 19 patients. In 17 patients the diagnosis was based on clinical examination and use of relevant investigations. Cytological assessment was the basis of diagnosis in 10 patients and in the remaining 130 patients histological confirmation of WT had been obtained.

Stage is recorded in the registration record as stage 1, localised; stage 2, regional or node involvement; stage 3, remote or diffuse metastases. The relationship between this system and that of the NWTS is shown in Table 1. Tumour stage, classified by the tumour registry, was available for 174 patients (98.3%). The majority of patients were stage 1 (50.6%), with 28.7% stage 2 and 20.7% stage 3.

Management aim was recorded for 163 patients (92.1%) and included 14 patients who received no treatment beyond diagnostic procedures. Treatment was considered palliative in 40 patients while in the remaining 123 cases curative therapy was attempted. Patients were not treated on the grounds of age (1 case, aged 83 years), extent of disease (10), general condition (1) and incidental finding during post mortem examination (1). One patient was excluded as treatment was undertaken outside New Zealand. Treatment consisted of surgery alone (32), or in conjunction with chemotherapy (29), radiotherapy (70) or both chemotherapy and radiotherapy (25). Radiotherapy and chemotherapy were individually employed in 1 patient and conjointly used in an additional 5 patients.

Sixty-six patients presenting with WT after 1976 were included in the series. With all these patients, diagnosis was made following histological examination of biopsy material or the resected specimen and 8 patients (12%) presenting after 1976 were reported as having anaplastic histology. The aim of treatment provided to this group of patients was considered palliative in 11 cases and curative in 52 cases. The treatment modalities of patients presenting before 1977 and after 1976 are compared in Table 2.

Survival data

Eighty-eight patients (50.3%) were alive at the end of 1990. The mean follow-up period for this group was 13.8 years and the 1 and 5 year actuarial survival rates were 66.7% and 52.5% respectively. The mean survival interval for the deceased patients was 15 months. As seen in Figure 2, there was a significant difference in survival between patients presenting prior to 1977 (5-year survival rate 36.4%) when compared with post-1976 patients (5-year survival rate 78.3%, $P<0.0001$).

Univariate analysis showed sex and ethnicity had no significant association with survival. Age at

Table 1 Relationship between National Cancer Registry and NWTS Stage

National Cancer Registry Stage	*NWTS Stage (D'Angio et al., 1989)*
1 Localised	I Tumour limited to kidney and completely excised
2 Regional or localised node involvement	II Regional extension of tumour beyond kidney and completely excised
	III Residual non-haematogenous tumour confined to abdomen
3 Remote or diffuse metastases	IV Haematogenous metastases

Table 2 Comparison of Treatment Modalities Employed in New Zealand pre- and post-NWTS

Treatment modality	*Pre-1977*	*Post-1976*
S	19	13
SC	4	25
SR	67	3
SCR	7	18
C	0	1
CR	2	3
R	1	0
Nil	11	3
Total	111	66

S, surgery; C, chemotherapy, R, radiotherapy

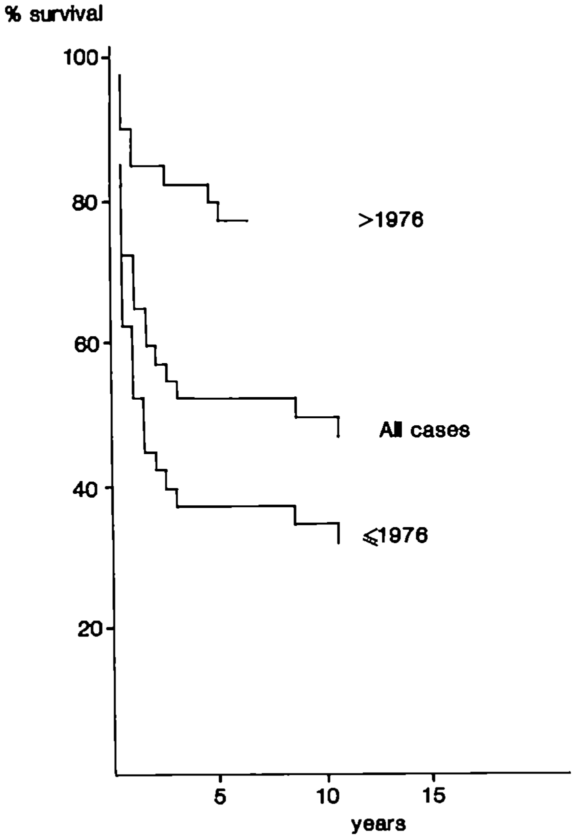

Fig. 2 Kaplan-Meier survival curve for all cases and those presenting ≤ or > 1976.

presentation of under 1 year predicted a poorer survival when compared with patients over 1 year of age (5-year survival rates 78.2% and 48.6% respectively, $P=0.03$).

Tumour stage was a significant predictor of survival (Fig. 3) ($P=0.0002$) and the aim of treatment showed a strong correlation with survival in patients presenting both before 1977 and after 1976. In patients where the stated aim of therapy was curative, the 5-year survival rate for patients presenting before 1977 was 47.8% compared with 80.7% for patients presenting after 1976 ($P=0.0001$). Of the deceased patients in each of these categories, the mean survival was 16.3 months for the former and 16.2 months for the latter group.

Multivariate analysis showed patients' age and symptom interval, stage of tumour at presentation and presentation prior to 1977 and after 1976 to be significant and independent predictors of survival (Table 3).

Discussion

Wilms' tumour is a rare form of malignancy that has gained in importance owing to the advent of successful management programmes. The tumour predominates in the paediatric age group and in white patients in the United States has an annual incidence of 7.1 cases per 10^6 population. This incidence is similar to that found in the present study and also to that reported from the United Kingdom (Breslow and Langholz, 1983).

The sex incidence as reported in the first NWTS (D'Angio *et al.*, 1976) showed a predominance of females over males. This trend was also found in data from the Surveillance, Epidemiology and End Results (SEER) programme (Breslow and Langholz, 1983) which collected cases from the United States from 1973 to 1977. Our data differ from this as we have recorded an almost equal sex distribu-

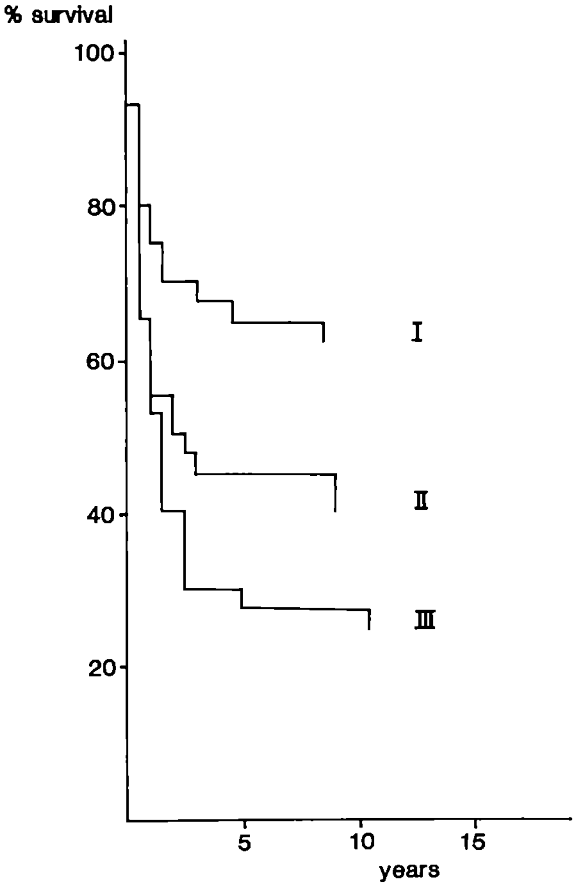

Fig. 3 Kaplan-Meier survival curve: tumour stage at presentation.

Table 3 Multivariate Analysis Showing Variables Independently Associated with Survival

Parameter	*Groups*	*DF*	χ^2	*P*
Date of presentation	$\leqslant$ and $>$ 1976	1	4.236	0.0396
Age	Continuous data	1	7.951	0.0048
Symptom interval	Continuous data	1	10.281	0.0013
Stage	I,II,III	2	17.686	0.0001

tion, as was reported from registries contributing to the first 4 volumes of Cancer Incidence in Five Countries (CI-5) (Breslow and Langholz, 1983).

The mean age at presentation in the present series is slightly less than that reported in the United States, although the finding that female patients are slightly older than males at the time of diagnosis is consistent with the findings from other series (Breslow *et al.*, 1988). Comparision of tumour stage at presentation between the present series and that recorded by both the first and second NWTS (D'Angio *et al.*, 1976, 1981) suggests that in New Zealand patients tend to present with more advanced disease despite a younger age at diagnosis. This variation is further accentuated by the staging options provided for in the second NWTS, which permitted upstaging for patients considered to be at higher risk of recurrence due to age or unfavourable histology. The greater proportion of National Cancer Registry stage 3 tumours may be explained in part by the absence of a category for bilateral disease. In a small regional series of patients reported from New Zealand, it was found that bilateral tumours formed 20% of cases (Delahunt *et al.*, 1990). However, this incidence was not reflected in a larger series from Australia where bilateral tumours were found to comprise only 1.5% of patients with WT (Hutson *et al.*, 1983). A further explanation for the higher proportion of advanced disease found in this study may be the relatively greater number of patients with anaplastic histology, as this poor prognostic indicator was found in only 4% of white patients in the United States (Beckwith, 1986).

The advent of the NWTS has had a major effect on the management of WT and this impact is shown in the present series. Before 1977, the diagnosis of WT was made without histological confirmation in almost 33% of patients, while after this date all diagnoses were made following tumour biopsy. It has been shown that a 5% error occurs where WT is diagnosed on clinical and radiological findings alone and because of this the NWTS recommended histological confirmation of the diagnosis prior to treatment (D'Angio *et al.*, 1976). In the current series this is reflected in the apparent increase in incidence following the publication of the initial NWTS.

The intent and method of treatment for WT show considerable diversity over the period of this series, with curative therapy being more frequently attempted in patients presenting after 1976. The treatment options reflect the recommendations of the first and second NWTS, with less emphasis on the use of radiotherapy, which has been shown to be of no additional benefit to younger patients or those with localised disease.

There was a dramatic improvement in survival in those patients presenting after 1976, with overall rates being similar to those reported elsewhere (D'Angio *et al*,. 1976, 1981, 1989). In those patients from this group in whom curative therapy was attempted the survival rate was even higher, further emphasising the success of the NWTS protocol. Of interest is the almost equal survival interval for patients actively treated both before 1977 and after 1976, where death occurred despite an attempted cure. The poor outcome in these cases suggests the existence of an aggressive group of WTs which are likely to progress despite adequate therapy.

Multivariate analysis of data showed patients' age at presentation, symptom interval and tumour stage to be of prognostic significance independent of treatment, determined as presentation either prior to 1977 or after 1976. The first NWTS also demonstrated age at presentation to be of prognostic significance, with those less than 2 years of age having a more favourable outcome than older patients (Breslow *et al.*, 1978). In our series this improved survival was independent of stage, suggesting that in younger patients WTs follow a more benign course.

Both symptom interval and tumour stage relate to tumour proliferation and dissemination, although the independent significance of these 2 parameters on survival indicates that symptom interval may be more dependent on tumour bulk than tumour spread. Staging has been shown to be of importance in assessing survival in cases of WT, as patients presenting with evidence of metastases have a poorer prognosis regardless of histology and despite aggressive treatment (D'Angio *et al.*, 1981). Our finding that patients in New Zealand have a tendency to present with more extensive disease emphasises the importance of early detection of

WT. Patients with localised disease have a potentially curable malignancy. However, if diagnosis is delayed then the likehood of a favourable outcome is significantly reduced.

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Continent Cutaneous Diversions in Children: Experience with the Mitrofanoff Procedure

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Summary—Continent cutaneous diversions with a urinary reservoir emptied by clean intermittent self-catheterisation (CISC) using a non-refluxing conduit—the Mitrofanoff principle—were carried out in 10 children. Their age range was 3.9 to 17.1 years (average 12.2). The underlying diagnoses were ectopia vesicae (7), myelodysplasia (2) and a cervical cord injury secondary to birth trauma (1). The indications were incontinence secondary to poor bladder neck resistance in 8 children and an inaccessible urethral orifice in 2. The catheterising conduits used were the appendix in 9 and a vascularised gastric tube in 1. Eight children are bone-dry with CISC. Another child needed a reoperation following dehiscence of her bladder neck closure. The other child has an intact bladder neck and urethra and occasionally leaks overnight.

Mitrofanoff diversions are a reliable means of continence with CISC. This means of urinary diversion can be permanent or temporary in children who cannot or will not catheterise urethrally. Elective appendicectomy in children with potential urinary incontinence or complicated urogenital anomalies is not recommended.

With the introduction of clean intermittent self-catheterisation (Lapides *et al.*, 1972) and the failure of ileal conduits or ureterosigmoidostomy to prevent renal deterioration (Shapiro *et al.*, 1975; Silverman *et al.*, 1986), the emphasis on renal tract reconstruction has shifted towards preservation of the lower urinary tract in children as well as adults. Although the urethra is the logical route for successful catheterisation, musculoskeletal deformities and urogenital abnormalities may prevent regular complete emptying. Continent urinary diversions offer an alternative method of achieving continence in upper tract preservation (Goldwater and Webster, 1985). We report our experience with the Mitrofanoff principle (Mitrofanoff, 1980; Duckett and Snyder, 1986) of a catheterisable anti-refluxing channel with a cutaneous stoma in the management of selected children with urinary incontinence.

Patients and Methods

Over a 3-year period from February 1989 to January 1991, 10 children underwent a Mitrofanoff diversion at the Royal Manchester Children's Hospital. The age range was 3.9 to 17.1 years (average 12.2). Follow-up was from 6 months to 3.5 years. There were 5 males and 5 females with underlying diagnoses shown in Table 1. All children had radiological (ultrasound, micturating cystourethrography (MCUG) and radioisotope studies) and videourodynamc investigations (including occlusion cystometry) pre-operatively. Competence with CISC by the child and/or parents was essential before surgery was undertaken. The appendix was used as the catheterising conduit in 9 children. The other child had had a previous appendicectomy and a pedicled gastric tube was fashioned.

Continent appendicovesicostomies were performed on 2 children with urethral orifices inaccessible to CISC. One child had a neuropathic bladder and a female hypospadias. Perineal stimulation evoked intense adductor spasm. The second child had a poorly compliant neuropathic bladder, detrusor sphincter dyssynergia and upper renal tract decompensation. Postural deformities secondary to a thoracolumbar myelomeningocele precluded CISC via the urethral route.

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Table 1 Underlying Diagnoses

Patient	*Age (years)*	*Conduit*	*Diagnosis*	*Indication*	*Associated procedures*
NB	9.4	Appendix	Tetraplegia, birth trauma	Female hypospadias (adductor spasm)	—
ST	14.3	Appendix	Ectopia vesicae	Poor bladder outlet resistance	Bladder neck closure, previous colocystoplasty
LB	9.9	Appendix	Ectopia vesicae	Poor bladder outlet resistance	Onlay clam ileocystoplasty, bladder neck closure
CH	13 9	Appendix	Ectopia vesicae	Poor bladder outlet resistance	Onlay clam ileocystoplasty, bladder neck closure
IB	17.1	Appendix	Ectopia vesicae	Poor bladder outlet resistance	Onlay clam ileocystoplasty, bladder neck closure
MT	15.8	Appendix	Myelomeningocele	Postural deformities	Onlay clam ileocystoplasty
CC	3.9	Appendix	Ectopia vesicae	Poor bladder outlet resistance	Onlay clam ileocystoplasty, bladder neck closure
SC	8.3	Gastric tube	Myelomenigocele	Poor bladder outlet resistance (failed AUS)	Onlay clam ileocystoplasty, bladder neck closure
CF	15.8	Appendix	Ectopia vesicae	Poor bladder outlet resistance	Onlay clam ileocystoplasty, bladder neck closure
NH	13.7	Appendix	Ectopia vesicae	Poor bladder outlet resistance	Onlay clam ileocystoplasty, bladder neck closure

AUS = artificial urinary sphincter.

Seven other children selected for a urinary Mitrofanoff diversion had failed to respond to previous bladder neck surgery and had negligible bladder outlet resistance. In 1 girl with myelodysplasia an extruded artificial urinary sphincter was removed and she remained incontinent.

Operative Technique

Appendicovesicostomy

The procedure was carried out through a Pfannenstiel incision. Initially the bladder was not opened but mobilised circumferentially from its extraperitoneal bed. The appendix was then detached from its caecal attachment and patency was confirmed. The appendicular length had to be sufficient to allow an anti-refluxing intravesical tunnel as well as an acceptable cutaneous stomal position. The bladder was then opened in the coronal plane to the level of the trigone. The appendix was tunnelled into the bladder, through the posterior bladder flap. The bladder neck was divided and oversewn in 8 patients with interrupted 4/0 PDS and the suture lines were separated by a vascularised greater omental plug. Care was taken to maintain vascularity to the anterior bladder flap with this manoeuvre. To ensure a taut, straight conduit the detrusor entry site of the conduit was fixed to the adjacent muscle. The cutaneous stoma was positioned subsequently. A suprapubic catheter was inserted through the anterior bladder flap and a LO FRIC catheter (Astra Heditec, Holndal, Sweden) passed through the appendix.

Vascularised gastric tube method

A cuff of gastric antrum was fashioned on the right gastroepiploic arterial pedicle (Borzi and Gough, submitted for publication).

Onlay "clam" ileocystoplasty (Bramble, 1982) was performed in children requiring bladder volume enhancement at this stage of the procedure.

All children had a stomal V-plasty to ensure an adequate calibre of the cutaneous opening. Deficiencies in conduit length were accommodated by fashioning a skin tube in 1 child and Boari flap reimplantation in 4 children.

Post-operatively the conduit catheter was removed on day 14 and regular catheterisation was commenced. The suprapubic catheter was subsequently removed when insignificant residual volumes were achieved and competence in the catheterising technique was established. This was usually after 7 days.

All children catheterise easily and there are no stomal or channel problems with the conduits. One catheterising channel accepts an 8F LO FRIC catheter, with all others accommodating a 10/12 F catheter.

Results

Continence

We have defined this as bone-dry at all times with CISC. Eight patients are continent without further surgery. One child required a second bladder neck closure before continence was obtained. The second child had no bladder neck closure, occasionally leaks *per urethram* at night but is happy with her result.

Radiological investigations

All children with non-dilated, non-obstructed upper urinary tracts pre-operatively remained unchanged on post-operative follow-up. One patient with renal decompensation secondary to a neuropathic bladder and detrusor sphincter dyssynergia had resolution of her upper tract dilatation and normal excretion curves on follow-up diuretic renography.

Urodynamic results (Table 2)

Nine children have had urodynamic assessments 6 months post-operatively. One child had normal bladder compliance and capacity and underwent an appendicovesicostomy for CISC access. Her follow-up urodynamic studies were essentially unchanged.

The remaining children in this series had preservation of the vesical remnant. These children had an insufficient bladder capacity and compliance to maintain upper renal tract well-being and continence pre-operatively and bladder augmentation was necessary. All children developed safe reservoir volumes (capacity at PDET <20 cm water) on post-operative videocystometrography, allowing 4-hourly CISC during the day and overnight dryness with fluid restriction.

Early complications

Of the 3 children with urinary fistulae, 2 leaked through the previous bladder neck closure and 1 via the old suprapubic site. With continued frequent catheterisation and augmentation expansion, 2 fistulae resolved within 6 weeks. The other child had extensive periurethral scarring from an eroded artificial urinary sphincter and there had been dehiscence of the initial bladder neck closure. A further urethral closure was carried out through the perineum.

Clot retention and partial dehiscence of the vesicointestinal anastomosis occurred on day 7 in 1 patient. Percutaneous nephrostomies for 3 weeks allowed healing without further surgery. He is continent on CISC and has safe reservoir volumes.

In 1 child a retained suprapubic catheter was removed endoscopically.

Late complications

One of our older children ruptured his ileocystoplasty 12 months after diversion. Poor compliance with CISC over the previous 24 h created a distended reservoir. Following laparotomy and oversewing of the perforation and urinary drainage,

Table 2 Urodynamic Results

	Pre-operative results		*Post-operative results*
Patient	*Leak pressure* (cm water)*	*Capacity** (ml)*	*Capacity*** (ml)*
NB	15	250	250–300
ST	<5	50	350
LB	<10	20	250
CH	<10	25	350
IB	<5	10	380
MT	100	120	420
CC	<5	15	260
CF	<5	35	380
NH	<10	25	300

* P Detrusor at urethal leakage.
** Capacity at leak pressure.
*** P Detrusor <20 cm water.

he remains continent with a stable upper renal tract.

Finally, 1 child had a laparotomy for an adhesional intestinal obstruction.

Discussion

The Mitrofanoff principle of an adequate urinary reservoir accessed by an antirefluxing catheterisable narrow channel has led to a wide array of anatomical arrangements in urinary reconstruction. We feel that the bladder remnant is the most reliable structure in which to reimplant the catheterising conduit, as well as the native ureters where necessary. In the present series all patients have either the bladder or the bladder with augmentation as the urinary reservoir. Others have used ileocaecum, caecum and colon successfully (Duckett and Snyder, 1986; Issa *et al.*, 1989; Woodhouse *et al.*, 1989). The appendix is the most commonly used narrow antirefluxing conduit for CISC. Alternatives such as ureter, vas deferens and fallopian tube have been reimplanted and exteriorised as a catheterising cutaneous stoma (Duckett and Snyder, 1986: Woodhouse *et al.*, 1989; Dykes *et al.*, 1991). All are reliable antirefluxing channels.

Vascularised stomach has a proven role in lower urinary tract reconstruction (Leong, 1978; Adams *et al.*, 1988). One child in this series had a pedicled gastric tube based on the right gastroepiploic artery. There were no problems with reconstruction, mobilisation and positioning and it continues to be a successful catheterising channel. There are no skin changes after 9 months follow-up.

To avoid difficulty with intubation the catheterising conduit must be taut, have a straight course and its position must not alter with the phases of filling and emptying of the urinary reservoir. Reducing redundancy, fixation of the conduit to the anterior abdominal wall and further fixation of its entry point extravesically to muscle have been shown to create a reliable accessible channel for CISC. It is recognised that stomal stenosis can be troublesome (Montfort *et al.*, 1984). We used skin flaps routinely and often retained the wider caecal cuff as the cutaneous stoma. Inadequacy of absolute length of the appendix did not preclude its use. Tubularised skin flaps and Boari bladder flaps compensated for insufficient length. The combination of the Boari flap with an onlay ileocystoplasty was problem-free. All 4 children maintained their antirefluxing capacity with bladder filling.

As segments of the gastrointestinal tract are commonly included in the urinary tract during reconstruction, the potential for malignant change must be considered (Stone *et al.*, 1987; Golomb *et al.*, 1989). Regular surveillance in the intermediate and long term will be necessary (Filmer and Spencer, 1990). We discovered while removing a retained suprapubic catheter that most of the urinary reservoir can be accessed with a rigid scope via the catheter channel. Flexible endoscopy would enhance the ease of visualisation.

Delayed rupture of an augmentation cystoplasty is often difficult to diagnose and can have potentially fatal consequences (Elder *et al.*, 1988; Rushton *et al.*, 1988; Sheiner and Kaplan, 1988). Abdominal pain, vomiting, unexplained sepsis and anuria with or without peritoneal irritation are strongly suggestive of the clinical diagnosis in any child with an enterocystoplasty. Occasionally the serum creatinine may be grossly elevated from peritoneal reabsorption. Cystography has been shown to be unhelpful in confirming the presence and site of the perforation. Ultrasound demonstrates free intraperitoneal fluid but its significance in the presence of a ventriculoperitoneal shunt is uncertain. Although there are many suggested aetiologies (Rushton *et al.*, 1988), retention of urine from incomplete emptying would seem to be the most likely precipitating factor. The importance of compliance with regular CISC cannot be overstressed. Greater awareness of this complication in at-risk patients with a good clinical history should encourage earlier intervention, as was carried out in our patient. Each patient wears a medical tag identifying them as having a continent diversion.

As can be seen from our series and those of others (Weingarten and Cromie, 1988; Dykes *et al.*, 1991), division of the bladder neck is not an absolute requirement in urinary Mitrofanoff diversions. Bladder neck closure seems justified in a child with multiple failed bladder neck repairs, poor quality periurethral tissue and inadequate bladder for further bladder neck reconstruction. Conversely, when sufficient urethrovesical competence is documented and transurethral catheterisation is precluded (*e.g.* inaccessible urethral meatus, urethral hypersensitivity), the urethra can remain intact. Thus the Mitrofanoff principle can be applied as a temporary as well as a permanent means of urinary diversion.

All other continent external urinary diversions, such as the Kock and Mainz pouches and caecal reservoirs, use long bowel segments and often include the ileocaecal valve. This may be critical in the context of a child with a neuropathic bowel. The continence effect is dependent on the ileocaecal valve or an intussuscepted ileum. Dehiscence of the valve mechanism often produces an unacceptable revisionary rate (Goldwater and Webster, 1985). Although these forms of continent diversion have a place, the Mitrofanoff principles involve less bowel segments, easy access to the urinary reservoir with CISC and a more reliable antirefluxing mechanism.

Urinary incontinence compounds the social problems of a child who often already suffers other physical handicaps. Continent Mitrofanoff urinary diversions are a reliable way of achieving dryness and maintaining upper renal tract integrity in selected children with urinary incontinence who cannot or will not regularly catheterise urethrally. The practice of elective appendicectomy in such children should be condemned.

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Epispadias Surgery—Belgrade Experience

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Summary—From 1987 to 1991, 46 patients underwent surgical treatment for epispadias. Of these, 14 had isolated epispadias and 22 had epispadias within the exstrophy/epispadias complex. The patients ranged in age from 6 months to 20 years. To correct the genital aspect of the anomaly the basic principles of Ransley's technique were used. In addition, the island flap technique was used for the most severe, so-called "cripple" form. In patients with exstrophy/epispadias complex, only elongation of the penis was performed during primary reconstruction, while the correction of epispadias, using the above techniques, was performed in the second-stage operation. Complications occurred in 6 patients.

The operative management of epispadias represents a great challenge in genital surgery. With or without bladder exstrophy, it requires a highly specialised approach. Several techniques are available but none is fully applicable in all cases (Ransley, 1988; Ransley *et al.*, 1989; Snyder, 1990). The procedure used in this department developed from our own ideas and concepts plus those of other authors, primarily Ransley (1988), Ransley *et al.* (1989) and Duckett (1977).

Patients and Methods

Between 1987 and 1991, 46 patients, aged from 6 months to 20 years, underwent epispadias surgery. Of these, 14 had isolated epispadias and 22 had epispadias with bladder exstrophy. The patients with the mildest glanular form of epispadias were excluded from the review. Epispadias was classified as follows: epispadias without incontinence (n = 8); epispadias with continence (n = 10); epispadias/exstrophy complex (n = 22); epispadias "cripple" form (n = 6).

The aim of the review was the correction of the genital aspect of the anomaly; urinary incontinence, as a separate and complex problem, was excluded. The timing of surgery depended on the severity of epispadias, penile size and urinary incontinence. In most cases testosterone was applied locally prior to surgery in order to enlarge the penis and improve its vascular supply.

Operative principle

The surgical approach varied according to the individual but the following basic procedures were used in most patients: mobilisation of the epispadiac urethra with rudimentary corpus spongiosum and its complete separation from the corpora cavernosa; preparation of the lateral neurovascular bundles; resection of the dorsal chordee—dorsal chordectomy; mobilisation of the corpora cavernosa up to their attachment at the pubic bones; tubularisation of the urethral plate and its ventral transfer; correction of the dorsal curvature, cavernoso-cavernosostomy using the corporeal rotation technique of Koff and Eakins (1984) or Ransley (1988); glanuloplasty as described by Ransley (1988); reconstruction of the peno-pubic angle using local pubic skin flaps (Kramer *et al.*, 1986) and reconstruction of the penile skin by the use of vascularised pedicle skin flaps; correction of the relationship between the penis and the scrotum, with approximation (Figs 1–5). In epispadias associated with bladder exstrophy, the following procedures were used to elongate the penis during primary reconstruction: mobilisation of the corpora

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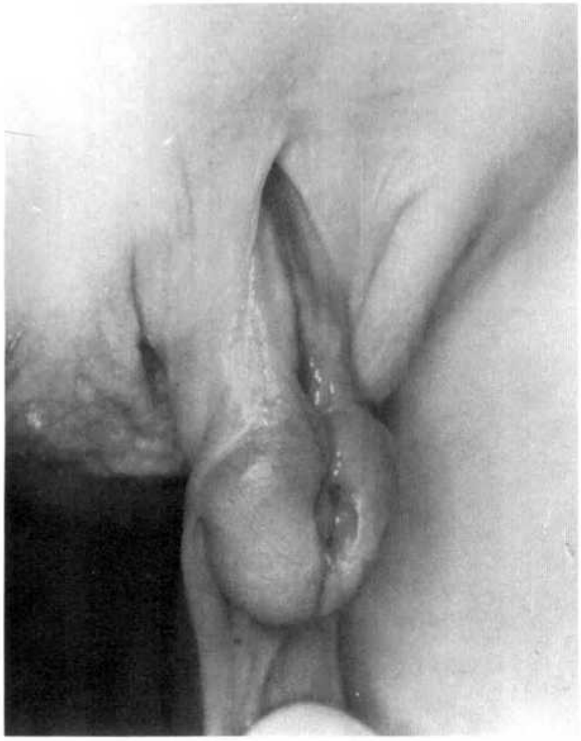

Fig. 1 Peno-pubic epispadias. Pre-operative appearance.

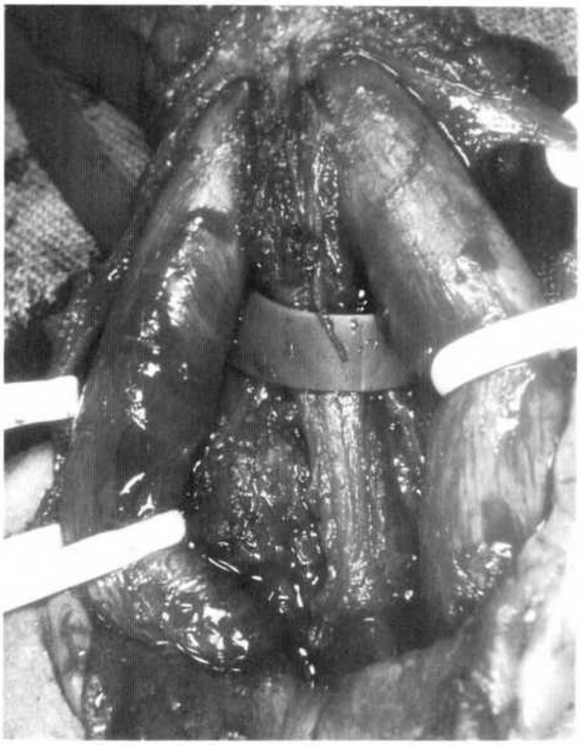

Fig. 2 The epispadiac urethral plate is mobilised and cavernous bodies and neurovascular bundles are dissected. Dorsal and ventral aspect.

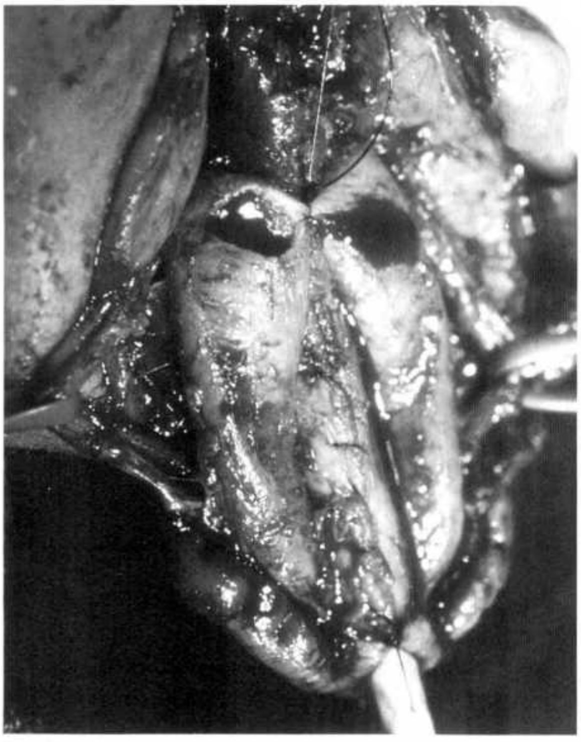

Fig. 3 After urethral plate tubularisation and its transfer to the ventral aspect of the penis, cavernoso-cavernosostomy and corporeal rotation are performed to correct dorsal curvature.

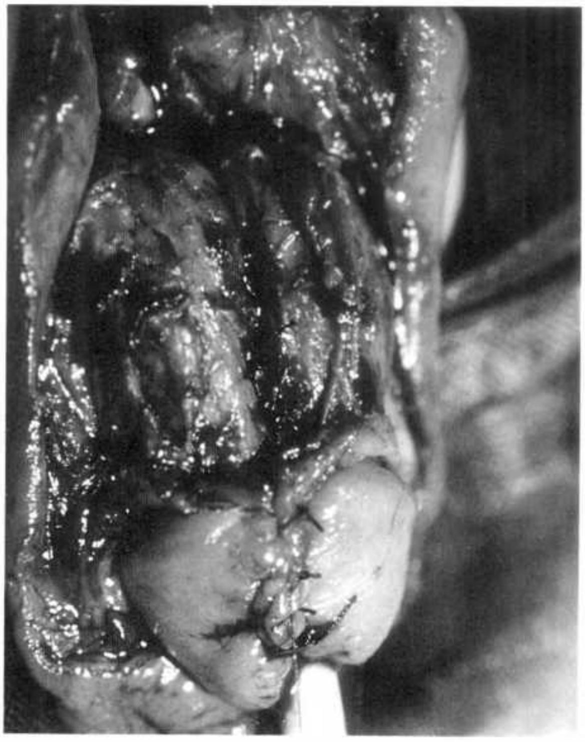

Fig. 4 Closure of glans and complete approximation of corpora cavernosa. The neurovascular bundles are localised on the dorsum of penis.

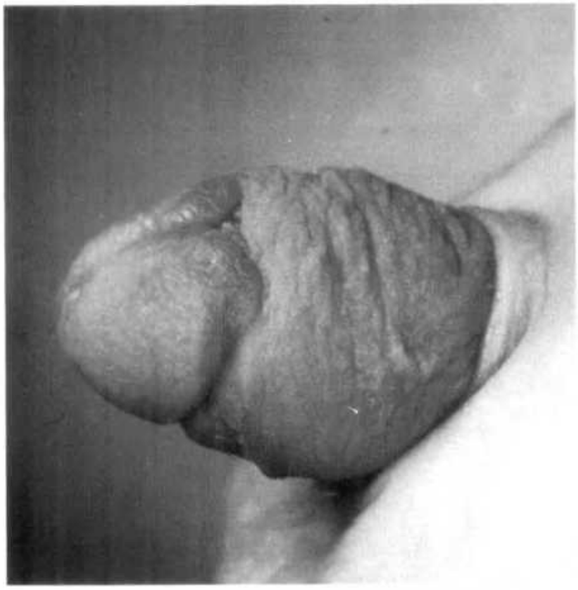

Fig. 5 Post-operative aspect of peno-pubic epispadias.

cavernosa up to their attachment at the pubic bones; elongation of the epispadiac urethral plate by means of para-exstrophy skin flaps and approximation of the corpora cavernosa as a result of anterior pelvic osteotomy and closure of the pelvic ring. Anterior pelvic osteotomy with symphyseal approximation eliminates an unsatisfactory penopubic angle. In the epispadias "cripple" form, caused by previously treated epispadias with resultant severe damage to the urethra, the island skin flap technique was used to form the neourethra (Thomalla and Mitchell, 1984). The urethra was usually formed from the ventral prepuce, when present; otherwise the ventral part of the penile body was used (Figs 6 and 7). The remaining procedures were as previously described. Urinary drainage, splinting of the new urethra and compressive bandages were employed in the usual manner.

Results

Follow-up ranged from 6 months to 4 years. Of the 46 patients, satisfactory results were achieved in 40, *i.e.* a straight penis angulated downwards in the standard position with the urethra positioned vertically and opening at the top of the glans. In infants the penile length was satisfactory when compared with the normal population, although the cosmetic appearance differed slightly from the usual aspect of circumcised patients. In 7 postpubertal patients the length of the penis ranged from 8 to 12 cm; 4 of these patients had satisfactory sex, 5 had normal antegrade ejaculation and 2 were without ejaculation, probably due to injury during previous surgery elsewhere.

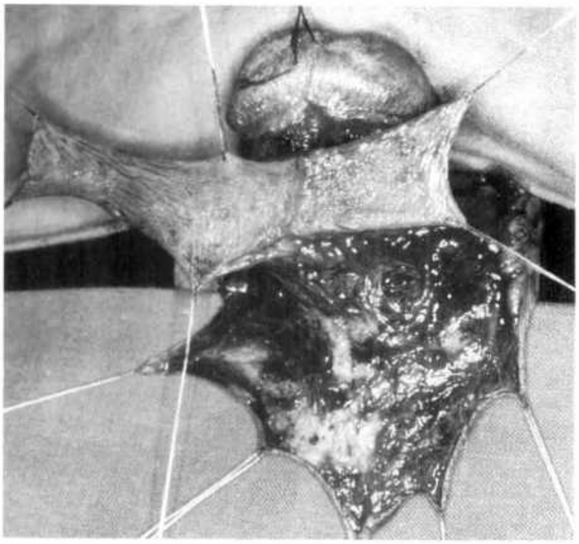

Fig. 6 Island skin flap technique to form neourethra.

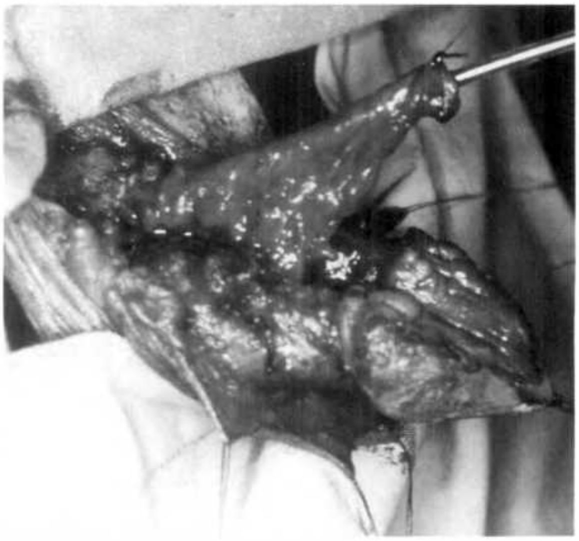

Fig. 7 Island skin flap tubularisation.

The following complications developed in 6 patients: 2 urethral diverticula following the island flap technique, 3 urethral fistulae and 1 dorsal curvature of the penis which was resolved by further surgery.

Discussion

Surgical management of isolated epispadias or epispadias associated with bladder exstrophy is a complex problem and each case must be approached individually. However, some basic surgical principles may be used in most patients, particularly in severe forms of isolated epispadias (Ransley, 1988; Ransley *et al.*, 1989). When used in highly specialised centres the technique gives the best results. Its principles are simple. The epispadiac penis is separated down to its anatomical segments, *i.e.* epispadiac urethral plate, lateral neurovascular bundles and corpora cavernosa, which are then joined to form normal anatomical relations, thus correcting the main problem of penile length, dorsal penile curvature and urethra. The unsatisfactory peno-pubic angle, whose correction represents a significant improvement, is successfully resolved in 2 ways: in severe forms of isolated epispadias by the use of suprapubic sliding skin flaps on submucosal tissue and Scarpa's fascia, and in epispadias associated with bladder exstrophy by the use of anterior pelvic osteotomy and approximation of the pubic bones in conjunction with osteosynthesis (Frey and Cohen, 1989). Anterior pelvic osteotomy permits approximation of the corpora cavernosa and concurrent penile lengthening. The highly positioned penis in relation to the scrotum is treated by means of local skin flaps. In other operative techniques, among which the island skin flap is most frequently used to form the neourethra, the results are generally poor. This has been particularly evident in our patients, especially those treated before 1987, when the procedure described by Ransley (1988) and Ransley *et al.* (1989) had not yet been used. It must be pointed out that we began to use this technique prior to its being reported in the literature. It is most efficient when used to treat the more severe forms of epispadias and epispadias associated with bladder exstrophy. However, the complications associated with this technique, although less frequent than those found with other techniques, indicate that further improvements are necessary in the surgical management of epispadias.

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Bladder Exstrophy and Anterior Pelvic Osteotomy

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Summary—Between August 1988 and December 1991, 36 children with bladder exstrophy underwent surgery for primary bladder reconstruction. Each child was either untreated or had already been treated unsuccessfully. The operative technique involved bilateral osteotomy of the superior ramus of the pubic bone. In infants the cartilaginous ischiopubic junction, acting as an articulation, allowed symphyseal approximation, while in older children this was achieved by fracture of the inferior ramus of the pubic bone. The bladder was either closed or, in most cases, the exstrophic bladder plate was inserted deep into the pelvis, allowing subsequent epithelialisation of the bladder and further formation and growth. Follow-up up for 3.5 years showed bladder capacities of 40 to 150 ml. Some patients underwent an additional augmentation enterocystoplasty. Primary bladder reconstruction remained uncompromised in 7 patients who developed moderate (and 1 complete) rediastasis of the pubic bones. All exstrophic bladders are reconstructible, particularly in older children.

Primary reconstruction of bladder exstrophy with or without posterior iliac osteotomy has not given satisfactory results in our patients, and in older children the results were particularly poor. Thus we found the resports by Frey and Cohen (1988, 1989) of great interest as they indicated a completely new approach to primary reconstruction of bladder exstrophy with the promise of more successful results. We began to use the technique shortly after publication of the first article and it is now our method of choice for primary reconstruction of bladder exstrophy.

Patients and Methods

Thirty-six patients, aged from 3 months to 12 years (27 male and 9 female), with bladder exstrophy were treated by anterior pelvic osteotomy between August 1988 and December 1991.

The indications for treatment were (1) previously failed bladder reconstruction (one or more operations) (n = 24), (2) untreated exstrophy (n = 9), (3) bladder neck reconstruction in conjunction with epispadias repair (n = 2) and (4) cloacal exstrophy (n = 1).

The only contraindication was hypoplasia, *i.e.* pubic bone aplasia. However, in a patient with unilateral hypoplasia of the superior ramus of the pubic bone anterior osteotomy was nevertheless successful.

Operative procedure

Mobilisation of the exstrophic bladder with wide mobilisation of the abdominal skin with subcutaneous tissue, and formation of the para-exstrophy skin flaps, formed the first stage of the procedure. Closure of the bladder, followed by reconstruction of the bladder neck and proximal urethra, comprised the next step but this was feasible in only 4 cases. It was not possible in the remaining 30 patients because of a small bladder plate and hypertrophied or polypoid bladder mucosa. In such circumstances the bladder plate was inserted deep into the pelvis, while only the bladder neck and proximal urethra were reconstructed by using the para-exstrophy skin flaps. The initial lengthening of the penis during primary reconstruction of the bladder facilitates several procedures: mobilisation

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of the corpora cavernosa up to their attachment to the pubic bones; separation of the neurovascular bundle from the corpora cavernosa; cutting of the urethral plate and its partially proximal mobilisation from the corpora cavernosa; elongation of the epispadiac urethra by para-exstrophy skin flaps; approximation of the corpora cavernosa due to anterior pelvic osteotomy and symphyseal approximation.

Osteotomy of the superior ramus of the pubic bone is the key to success in primary reconstruction of the exstrophic bladder. It is performed in the space between the adductor and pectineal muscles. Osseous retractors are inserted into the obturator foramen to protect the obturator nerve and blood vessels. Osteotomy is most often performed with an osseous chisel or a wire saw. Symphyseal approximation is possible in infants because the cartilaginous ischiopubic junction acts as an articulation. In older children the inferior ramus of the pubic bones is fractured during approximation of the superior ramus, thus enabling almost tension-free symphyseal approximation. Unless the inferior ramus of the pubic bones is fractured, symphyseal approximation is under considerable tension and there is a permanent tendency to diastasis. Symphyseal approximation causes a defect between the osteotomised superior ramus of the pubic bones. It may remain as such or may be bridged by a bone transplant, which was performed in 2 cases. A combination of wires, bolts and plates is used for osteosynthesis, which is easily performed and highly stable in older children owing to the strength and structure of their bones. In neonates and infants osteosynthesis is more difficult to perform and is less stable. After symphyseal osteosynthesis, adaptation and suture of the rectal muscles and abdominal wall soft tissue are performed mostly without tension. When bladder exstrophy is associated with cryptorchidism, orchiopexy is performed at the same time (Figs 1 and 2).

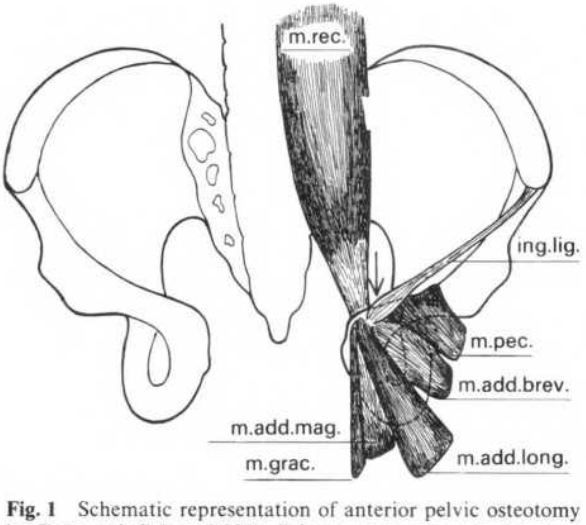

Fig. 1 Schematic representation of anterior pelvic osteotomy by Frey and Cohen (1989). Prior to osteotomy the inguinal ligament, pectineal, adductor and rectal muscles must be identified. The arrow indicates the site of osteotomy between the adductor and pectineal muscles.

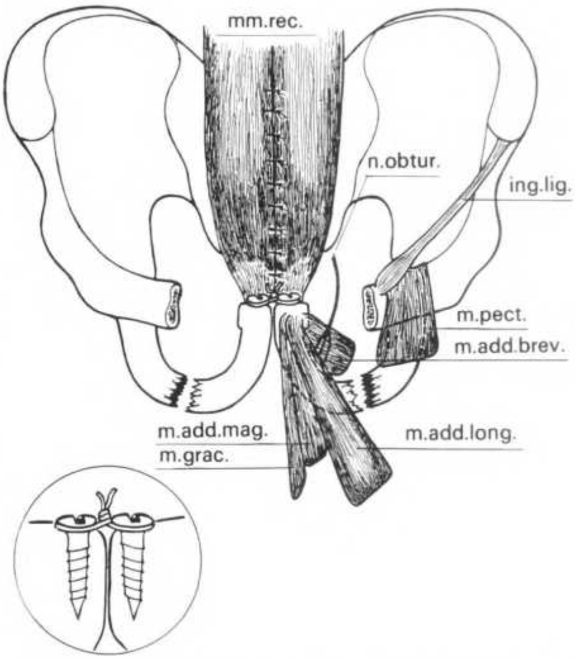

Fig. 2 Aspect after bilateral osteotomy of superior ramus of the pubic bone and osteosynthesis following complete symphyseal adaptation.

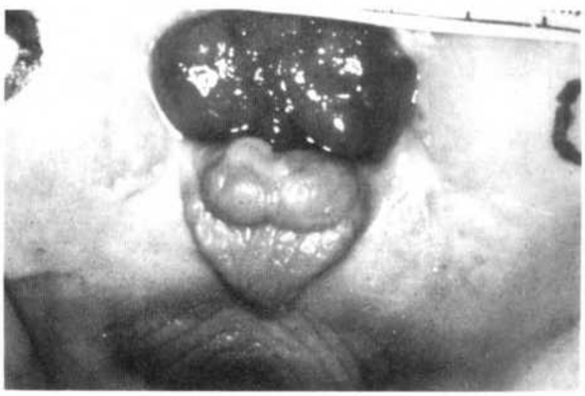

Fig. 3 Aspect in 5-year-old boy following several failed attempts at primary bladder reconstruction; small bladder plate with hypertrophic mucosa. Symphyseal diastasis is 10 cm.

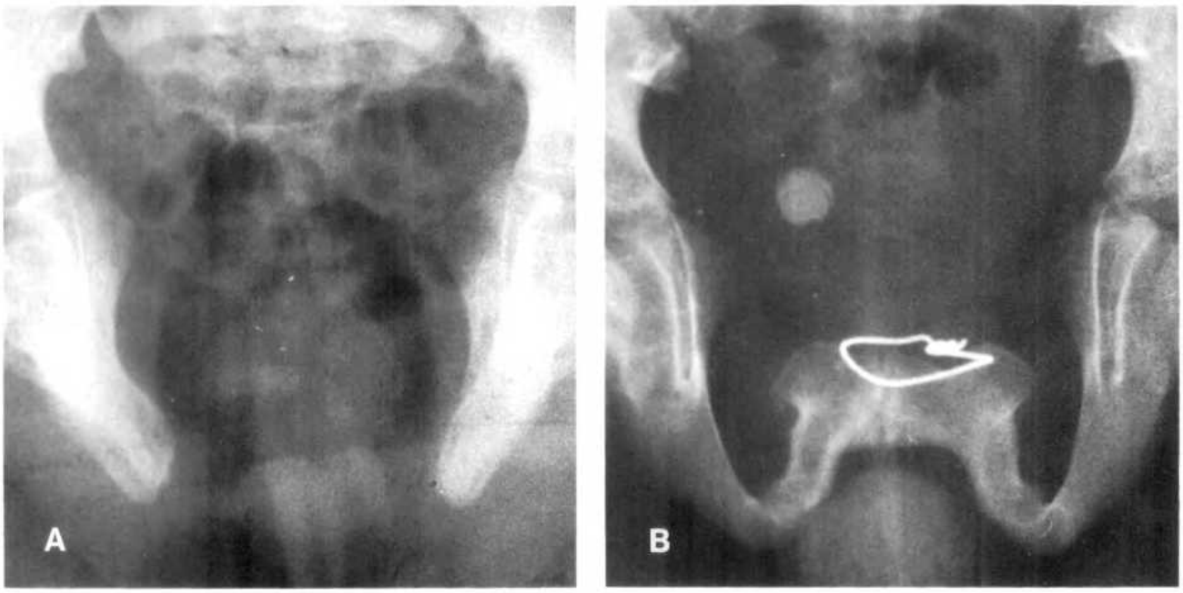

Fig. 4 (A) Plain X-ray showing symphyseal diastasis. (B) Plain X-ray after anterior pelvic osteotomy.

Urinary diversion is maintained by urethral splints or directly from the bladder for the next 2 to 3 weeks, and wound drainage for 1 week. Immobilisation is maintained for 4 weeks and walking is allowed after 6 weeks. Antibiotic therapy is given for 3 weeks.

Results

The patients have been followed up for 3 years and 5 months. In all cases a new bladder with a capacity of 40 to 150 ml was formed. When the bladder plate was placed in the pelvis, the new bladder was formed by secondary epithelialisation. Histologically, newly formed bladder was seen on the anterior wall, with hypotrophic muscle fibre surrounded by well developed connective tissue on the posterior wall and a marked muscular layer with some connective tissue. The small bladder capacity necessitated augmentation enterocystoplasty in 12 patients (Sigma or Mainz pouch) and the remaining patients await a similar procedure. Epispadias correction, as the final step in the management of the epispadias-exstrophy complex, was performed in 12 patients and continence was achieved in 8 without additional bladder neck reconstruction. A successful anti-incontinence procedure was achieved by combining the Young-Dees method with anterior pelvic osteotomy in 2 cases (primary reconstruction of the bladder neck in conjunction with augmentation enterocystoplasty had been performed in another hospital) (Figs 3–6).

The following complications were noted: bleeding from the obturator veins developed during surgery in 2 patients and was successfully treated; 3 patients developed partial wound dehiscence with formation of a vesico-cutaneous fistula which closed

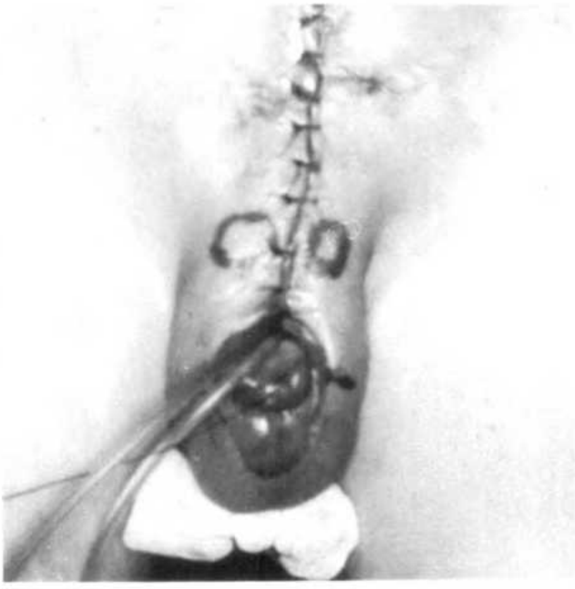

Fig. 5 Result following surgery. Bilateral orchiopexy was also performed because of cryptorchidism.

spontaneously; complete symphyseal rediastasis was noted in only 1 patient, while moderate rediastasis occurred in 7. Symphyseal rediastasis did not affect the final result of reconstruction of the bladder and anterior abdominal wall. A stable pelvic ring without compromised gait was achieved in all patients. Four children developed a hernia; in 1 child this was bilateral, resulting from a defect in the reconstruction of the inguinal part of the anterior abdominal wall. There were no cases of public bone osteitis.

Discussion

The results achieved by primary reconstruction of bladder exstrophy using anterior pelvic osteotomy have been substantially better than those obtained from other techniques (Jeffs *et al*., 1982; Mollard *et al*., 1986; Ransley *et al*., 1989; Snyder, 1990). A 3-year follow-up period has proved adequate to assess the efficacy of the method. Anterior pelvic osteotomy allows symphyseal approximation even in most severe cases (up to 12 cm diastasis), with tension-free rectus muscle approximation and reconstruction of the anterior abdominal wall. The method is particularly successful when previous surgery has failed, with or without polypoid bladder mucosa. Burying the bladder in the pelvis allows the formation of a new bladder by secondary epithelialisation developing from the bladder plate. In older children the procedure is easy because of the strength and structure of their bones. Fracture

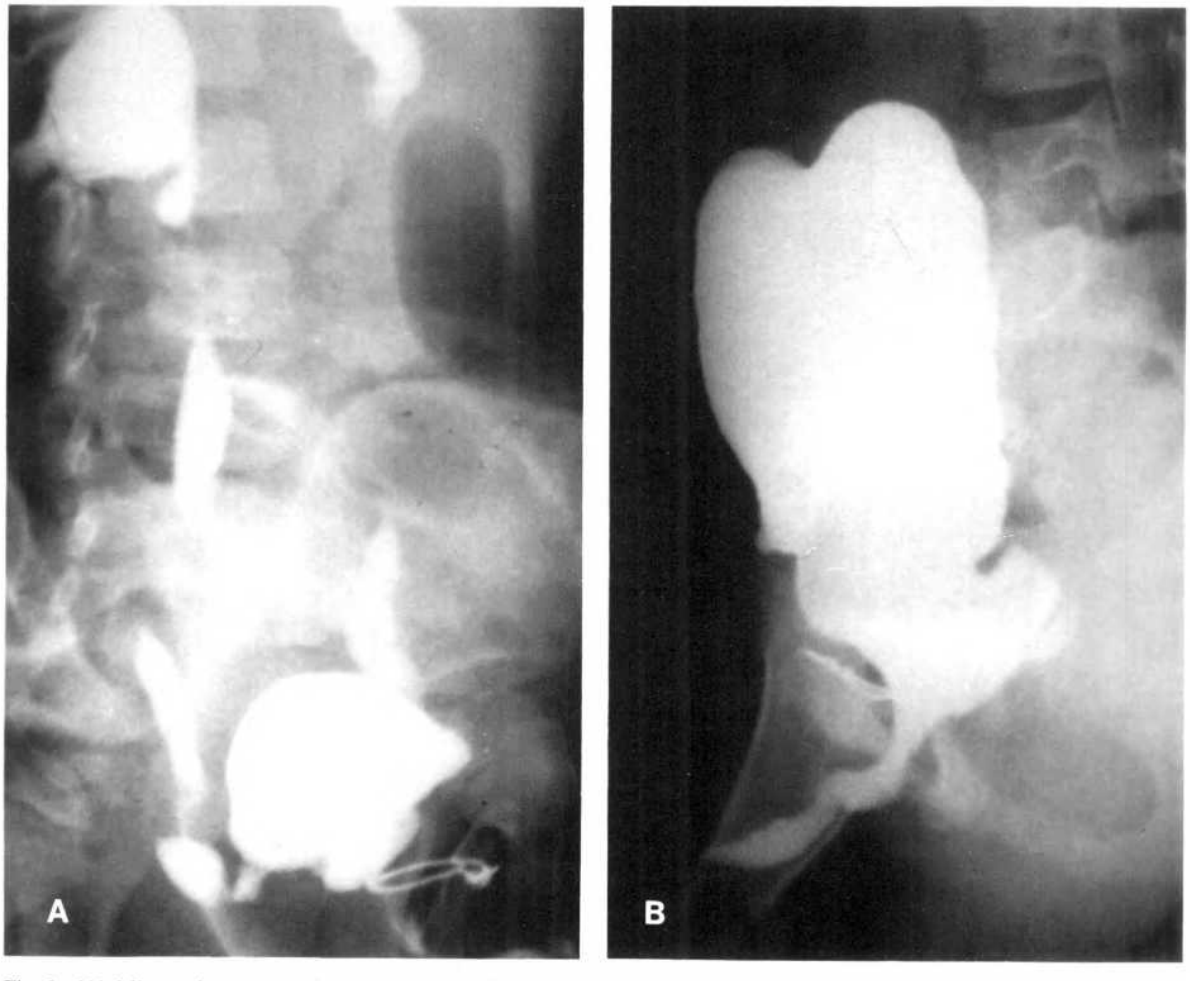

Fig. 6 (A) Micturating cystourethrogram (side view) 1 year after primary bladder reconstruction showing newly formed bladder created by secondary epithelialisation of bladder plate buried deep in the pelvis. New bladder capacity is 80 ml. Bilateral vesicoureteric reflux. Angulation of the neck and proximal urethra positioned below the symphysis. (B) Micturating cystourethrogram shows good bladder capacity following bladder augmentation (Sigma pouch).

of the inferior ramus of the pubic bones, following symphyseal approximation, is the key to tension-free approximation. In infants this leads to the formation of a cartilaginous ischiopubic junction, although this is continually under high tension. Rediastasis of the pubic bones often occurs in infants but does not compromise the method, and approximation of the anterior abdominal wall and formation of a new bladder were achieved in all cases. In our experience, the results of posterior pelvic osteotomy are unsatisfactory because most patients developed rediastasis, wound dehiscence and prolapse of the exstrophic bladder.

Pelvic ring reconstruction permits angulation of the bladder neck and proximal part of the urethra, which represents one of the stages in the anti-incontinence procedure. In addition to other procedures (mobilisation of the corpora cavernosa and neurovascular bundles, elongation of the urethral plate by para-exstrophy skin flaps, *etc*), approximation of the pubic bones permits elongation of the penis. The stability of the pelvic ring is good, gait remains uncompromised and the cosmetic appearance is satisfactory. Our experience shows that the defect between the osteotomised parts of the superior ramus of the pubic bones does not affect pelvic stability, thus making it unnecessary to bridge the defect with a bone transplant. The main disadvantage of the method is hernia, which may develop as the result of a large defect between the osteotomised parts of the superior ramus in the inguinal part of the anterior abdominal wall. Anterior pelvic osteotomy allows primary bladder reconstruction to be postponed until the child is between the first and the second year of life, when the best results can be achieved, and no gradation in the degree of reconstructibility of the exstrophic bladder is necessary. Each exstrophic bladder is reconstructible, regardless of grade, if anterior pelvic osteotomy is used. Despite these satisfactory results, however, the search must continue for better solutions.

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Results of Surgical Treatment in Children with Bladder Exstrophy

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Summary—A series of 42 children (30 boys and 12 girls) underwent surgery for bladder exstrophy between 1972 and 1989. Primary bladder closure was performed in 11 patients and was successful in 6. Four of these children are about 2 years old and so it is not yet possible to assess their continence. Ureterosigmoidostomy was performed in 35 children, one of whom was converted to cutaneous ureterostomy. Follow-up ranges from 2 to 20 years (average 9 years 3 months) and 50% of the patients are symptom-free. The most frequent problems were acidosis and urinary tract dilatation. Other complications, such as hypokalaemia and pyelonephritis, were seldom seen. Although ureterosigmoidostomy has some disadvantages, our patients have adapted well and lead a normal life.

Management of the bladder exstrophy patient presents a great challenge to the surgeon. Closure of the bladder is the ideal solution, but reconstructive surgery cannot create completely normal anatomy and physiology. We present our experience with bladder exstrophy patients in the 1970s and 1980s.

Patients and Methods

Between 1972 and 1989, 42 children (30 boys and 12 girls) underwent surgery for bladder exstrophy. Their ages at the time of the first operation ranged between 7 days and 18 years and they are currently aged between 2 and 34 years. Mean follow-up is 9 years 3 months. Eight children had associated anomalies: horseshoe kidney (1), duplex kidney (1), solitary kidney (1), ectodermal dysplasia (1), heart failure (1), vertebral anomalies (1), bilateral undescended testis (5).

Primary bladder closure. During the 1970s and in the early 1980s we had a strict policy for selecting children for bladder closure. Contraindications included those with a small bladder, with infection or leukoplakia on the bladder mucosa and those whose general condition was not good. Bladder closure was performed in 11 patients (9 in this institute and 2 in other hospitals; in the latter 2 cases the procedure was unsuccessful). Bladder closure was successful in 6 cases (in 3 following repeat procedures) (Table 1). The 9 patients treated here were between 7 days and 1 month old, except for one child who was 1 year old. The ureters were always stented for 14 days and a small feeding tube was placed in the bladder and led out through the urethra or through the wound. Osteotomy was not performed after 1970 because it did not lead to improved results. In our opinion the divergent pubic bones can be brought together easily because of the mobility of the sacroiliac articulation; it is important to secure the pubic bones with nylon sutures.

Urinary diversion. In children who were judged unsuitable for primary or repeat bladder closure, urinary diversion was performed; 35 children underwent this operation (24 boys and 11 girls); 24 were aged between 2 and 3 years, 10 between 3 and 6 and one boy was 18 years old. In each case a

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Table 1 Reconstructive Procedures for Bladder Closure in 6 Patients

Type of surgery	*No of operations*
Bladder closure (1 operation)	3
Reconstruction for complete bladder dehiscence	2
Reconstruction for partial prolapse	4

Table 2 Ureterosigmoidostomy: Outcome and Symptoms in 34 Patients

Free of symptoms	17 (50%)	
Chronic pyelonephritis	3	(50%)
Urinary tract dilatation	13	
Non-functioning kidney	2	
Impaired renal function	5	
Acidosis	15	
Hypokalaemia	4	
Hypocalcaemia	1	
Anal incontinence	0	
Mortality	0	

ureterosigmoidostomy was done. Examinations were carried out pre-operatively to establish anal continence and 8 children underwent surgery related to their bladder exstrophy. Three needed perineal/anal procedures prior to urinary diversion and this resulted in good anal continence. Five children had failed bladder closure; one of them had undergone bladder closure elsewhere, followed by abdominal wall reconstruction due to eventration and later a laparotomy for ileus. Ureterosigmoidostomy was followed by early complications in 5 children: paralytic ileus with partial wound dehiscence in 2 and acute pyelonephritis in 2. One boy developed urinary leakage from the abdomen on the eighth post-operative day; this was caused by bilateral dehiscence of the anastomosis between the ureter and the sigmoid and bilateral ureterocutaneostomy was done. Late post-operative complications necessitating surgery occurred in 3 cases: in 2 children a pyelonephrotic non-functioning kidney had to be removed and in one girl, 10 years after ureterosigmoidostomy, a laparotomy was performed for mechanical ileus caused by strangulation.

Results

Primary bladder closure. In all 6 children both the kidneys and the urinary tracts are normal, with no sign of urinary tract dilatation or infection. Four children are now 2 years old, so their continence cannot yet be established. Two boys (6 and 14 years old) have only partial continence and can void 60 and 100 ml respectively.

Urinary diversion. In all, 34 patients have ureterosigmoidostomies. All who underwent urinary diversion are alive and 17 patients (50%) are free of symptoms. Of the remaining 17 patients, 13 have some degree of urinary tract dilatation and 5 have chronic pyelonephritis for which 2 nephrectomies have been performed. Acidosis is minimal in 5 cases and moderate in 10. Hypokalaemia occurred in 4 patients, necessitating substitution. Transitory hypocalcaemia was seen in 1 child. All patients have good anal continence (Table 2).

Discussion

Several decades ago it was generally accepted that urinary diversion was the only solution to bladder exstrophy. Ureterosigmoidostomy was usually performed, but other forms of diversion appeared later and only a few bladder closures were carried out. The number of bladder closures increased gradually but even now, when most centres agree that it would be the most beneficial procedure, the percentage of diverted patients is still significant (O'Donnel, 1984; Connor *et al.*, 1988; De la Hunt *et al.*, 1989). In Great Britain and Ireland, 38 of 81 patients born between 1975 and 1985 were diverted (De la Hunt *et al.*, 1989). Urinary diversion is often necessary after bladder closure as a result of complications such as hydroureteronephrosis or stones. O'Donnell (1984) reported that 14/24 children were diverted. On the other hand, in the management of patients with failed exstrophy closure (Gearhart *et al.*, 1991) and in operative techniques designed to improve continence after bladder closure (Gearhart *et al.*, 1989; Hollowell *et al.*, 1991), further progress has been achieved. In the present study, 35/42 patients (83%) have diverted urinary tracts. The fact that most of our successful bladder closures were carried out in 1988 and 1989 reflects the changes in our approach to treatment and the changes in referral patterns to this institute. In the management of bladder exstrophy patients we have gained experience mainly with ureterosigmoidostomy and follow-up is sufficiently long for an opinion to be formed about the results. It is noteworthy that 50% of our patients are completely free of symptoms. Those who do have symptoms can be managed conservatively and all have an acceptable life style. Patients aged 6 to 18 years attend school, some are university students and those who have reached adulthood are all working. One patient gave birth to a child. Thus, although ureterosigmoidostomy has its disadvantages, it does enable patients to lead a normal life.

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Case Reports

Giant Hydronephrosis

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Giant hydronephrosis caused by congenital pelviureteric obstruction is uncommon. When it exists, however, the kidney and renal pelvis can extend across the midline and may occupy the entire abdomen, containing more than 1 litre of fluid (Friedland *et al.*, 1983). Most of the reported cases are sporadic and occur in infants and children. Urinary extravasation from giant hydronephrosis is rare and we believe that a combination of intraperitoneal extravasation with extravasation into the pleural cavity has not previously been reported.

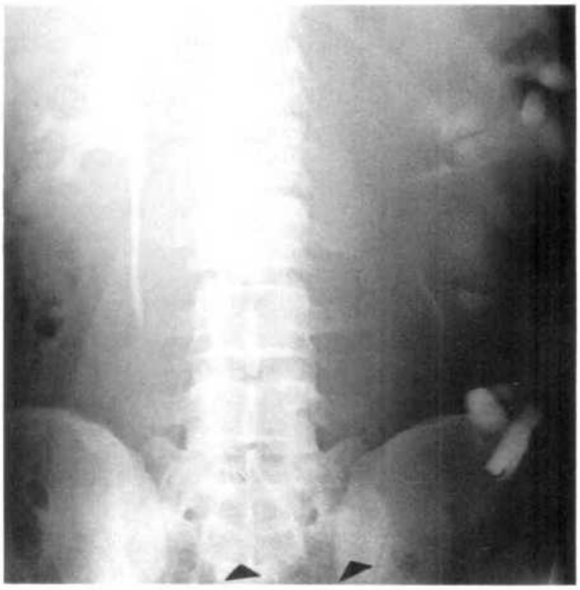

Fig. 1 Case 1. Intravenous urogram showing poor visualisation of dilated left caliceal system. The kidney extends from the diaphragm to below the iliac crest (arrows).

Case Reports

Case 1. A 27-year-old man presented with a 3-day history of progressive abdominal distension and constipation. Physical examination revealed a grossly distended abdomen. The upper margin of the swelling was at the level of the epigastrium and the lower margin was at the suprapubic region. It was mildly tender without rebound, and dull to percussion. A preliminary diagnosis of subacute intestinal obstruction was made.

Investigations showed normal levels of haemoglobin, white cells and ESR; electrolytes and liver function tests were within normal limits. The urine contained microscopic amounts of blood, a trace of albumin and a few pus cells. Intravenous urography revealed a normal right kidney but poor visualisation and massive dilatation of the left pelvicaliceal system. The kidney extended from the diaphragm to below the iliac crest, crossing the midline and measuring 7 vertebrae vertically (Fig. 1). An ultrasound scan of the abdomen showed a hydronephrotic left kidney. Computed tomography and dynamic renal studies confirmed a normal right kidney and a non-functioning, grossly enlarged and damaged left kidney. At operation the left kidney was exposed extraperitoneally through a standard twelfth rib approach. The hydronephrotic sac was thin and decompressed slowly using a trocar catheter; 12 litres of coffee-coloured urine were drained. The sac extended below the pelvis, compressing and displacing the intestine on the right side. The pelviureteric junction was stenotic. The patient made an uneventful recovery following nephrectomy.

Case 2. A 21-year-old man was admitted with colicky abdominal pain, abdominal distension, vomiting and difficulty in breathing. One week prior to admission he had had pain in the left hypochondrium accompanied by nausea and anorexia; otherwise he had been healthy and had no urinary symptoms.

On examination he was found to be toxic, dyspnoeic and acidotic, with a high fever. The abdomen was grossly distended and tender. There was particular tenderness in the left lower chest, which was dull to percussion. Investigations revealed the following: white cell count 31.9×10^3, ESR 95, serum creatinine 9.0 mg/dl and blood urea 336 mg/dl. Serum bicarbonate was 16 mEq/l and chloride 79 mEq/l. Chest X-ray showed a massive left pleural effusion (Fig. 2). Percutaneous aspiration of the abdominal cavity yielded 5000 ml of yellowish fluid and a left intercostal tube drained 3000 ml of fluid, with serum levels of creatinine and urea higher than in the blood. Abdominal ultrasonography showed the kidneys to be replaced by huge multicystic images with free fluid in the abdomen. IVU showed markedly delayed excretion of contrast material in the dilated left pelvicaliceal system. The left kidney extended from the diaphragm to the left lower quadrant and crossed the midline. There was no function in the right kidney. Computed tomography showed bilateral pelviureteric junction obstruction with giant hydronephrosis and much free fluid in the abdomen.

Bilateral percutaneous nephrostomy was performed; 11,500 ml of urine were drained from the left kidney and 500 ml from the right kidney. With hyperalimentation,

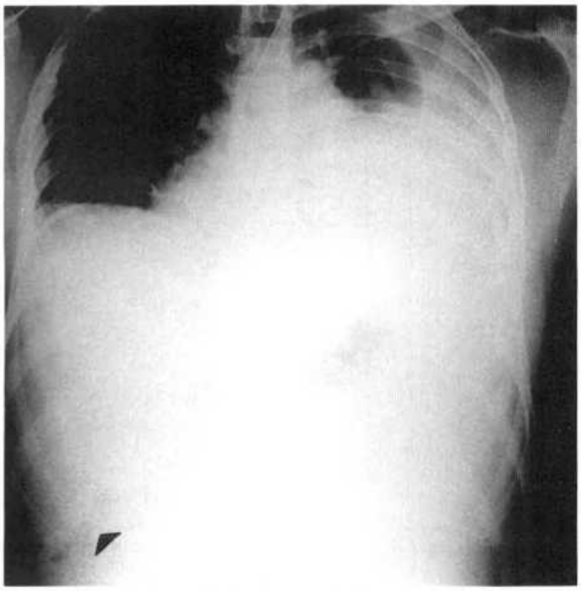

Fig. 2 Chest X-ray showing massive left pleural effusion. Below the right side of the diaphragm (arrow) the intraperitoneal fluid displaces gas-containing bowel towards and lateral to the liver.

correction of metabolic acidosis and antibacterial therapy the patient's general condition improved and renal function returned to normal. The left percutaneous nephrostomy continued to drain an adequate amount of urine but only a few ml were drained from the right side. Two weeks later a modified left Anderson-Hynes pyeloplasty was carried out. Six months later the patient was asymptomatic and his renal function has remained normal.

Comment

Hydronephrosis caused by pelviureteric obstruction does not always progress, but may increase rapidly and without warning in adult life (Hinman *et al.*, 1983). Most patients with giant hydronephrosis present with an abdominal mass which may cause respiratory distress, and occasionally with intraperitoneal urinary extravasation. This occurs most often in infants with primary obstructive megaureter, posterior urethral valves or vesicoureteric reflux (Krane and Retik, 1974; Cass *et al.*, 1981).

The most important aspect of management is early diagnosis with accurate pre-operative delineation of the anatomy of the affected kidney. In patients with urinary ascites and urothorax, early drainage allows the renal function to improve before appropriate surgical treatment is undertaken.

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Primary Malignant Melanoma of the Male Urethra

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Case Report

A 63-year-old man presented with a 9-month history of urethral bleeding. Retrograde urethrography demonstrated an irregular filling defect in the bulbous urethra (Fig. 1). Biopsy of the urethral tumour revealed malignant melanoma (Fig. 2).

Although total emasculation and bilateral inguinal and pelvic lymph node dissection were performed, and chemotherapy with dacarbazine, nimustine and vincristine was administered, the patient died 4 months after operation.

Comment

Primary malignant melanoma of the male urethra is rare; only 32 cases have been reported in the English literature (Paw-Sang *et al.*, 1988) and 7 in the Japanese literature (Yamamoto *et al.*, 1989).

Most patients were diagnosed in the sixth or seventh decade. Urinary symptoms were common and included a palpable mass, dysuria, bloody penile discharge and other voiding complaints. The most common sites were the fossa navicularis and the meatus, the occurrence rate in the proximal urethra being only 20%.

Radical surgery involving total penectomy with *en bloc* urethrectomy has been recommended for distal and proximal lesions, as the local recurrence

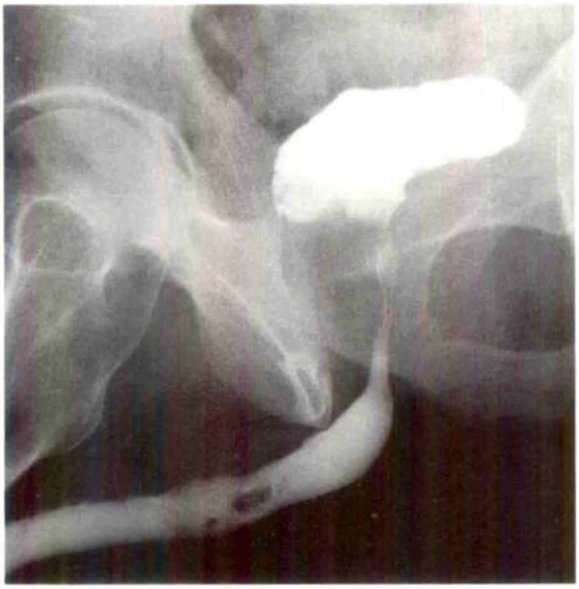

Fig. 1 Retrograde urethrography demonstrating irregular shadow defect on bulbous urethra.

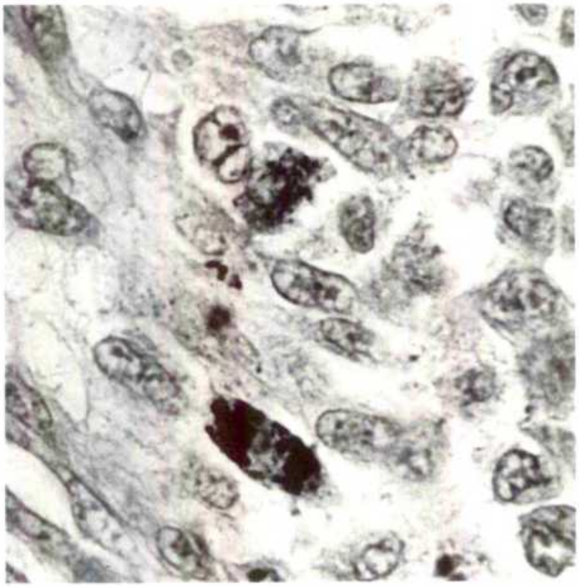

Fig. 2 Urethral tumour showing malignant melanoma. (Fontana-Masson's stain ×400).

rate after partial penectomy is high (Paw-Sang *et al.*, 1988). Cystoprostatectomy and pelvic lymph node dissection have also been used to treat lesions in the proximal urethra and the penoscrotal junction (Stein and Kendall, 1988). Radiology and chemotherapy have shown limited benefit, although they are indicated in patients with lymph node involvement and metastasis.

Despite aggressive therapy, patients with urethral melanoma have a poor prognosis. Only 9 of 40 patients (23%) were free of disease at the time of the reports, and most tumour-related deaths occurred within 3 years of diagnosis.

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Chylous Ascites following Retroperitoneal Lymph Node Dissection for Testis Cancer

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Chylous ascites is an uncommon complication following retroperitoneal surgery. We report a case of chylous ascites following retroperitoneal lymph node dissection for genitourinary cancer which responded to paracentesis and a medium-chain triglyceride diet.

Case Report

A 24-year-old male had previously undergone a right orchiectomy for malignant teratoma undifferentiated, staged IIC by CT scan. Cytoreduction had been attempted with several courses of combination chemotherapy (BOP/VIP) over a 3-month period. Repeat scanning had shown persistence and cystic transformation of the retroperitoneal mass. Retroperitoneal lymph node dissection was, therefore, performed via a transabdominal midline approach. An infrarenal dissection was performed and all macroscopic disease removed using the technique described by Donohue (1988). Histology showed foci of mature differentiated teratoma.

The patient was discharged after an uneventful recovery but was readmitted as an emergency 6 weeks later with progressive abdominal swelling, back pain and a 9.5 kg weight loss. Abdominal ascites was demonstrated by a fluid thrill and confirmed clinically by paracentesis, which yielded chylous fluid (protein 32 g/l, cholesterol 1.38 mmol/l; triglyceride 10.4 mmol/l; AFP <1 kU/l; HCG 4 IU/l; cytology: reactive change only; no growth on culture). Four litres of fluid were drained immediately, followed by a further 4 litres 8 h later. Serum cholesterol and triglycerides were normal on admission, as was albumin (41 g/l). Lymphopenia (0.4×10^9/l) was present on routine blood count, but this had been present since his original orchiectomy and during cytoreduction. Within 72 h of admission his total body weight had fallen from 75 to 64 kg, serum albumin to 31 g/l and a total of 11.5 litres of chylous ascites had drained. By day 5 his body weight was 59 kg and a total of 18.75 litres of ascites had drained.

On day 3 the patient was started on a medium-chain, low fat diet that provided a daily intake of 2280 kcal, 131 g protein, 14 g long-chain triglycerides and 60 g medium-chain triglyceride. Between days 6 and 10 the volume of ascites had reduced to approximately 0.7 litres/day of clear fluid. Triglyceride estimation of this fluid at the end of this period was 0.23 mmol/l (normal serum 0.2–2.0 mmol/l). The peritoneal drain was removed on day 11 after it ceased draining. The patient was discharged and remained on his diet for a further week. An ultrasound scan 2 weeks following discharge showed no evidence of reaccumulation of ascites, his weight having increased from 61.5 kg on discharge to 63.3 kg.

Comment

Chylous ascites occurs as a result of disruption of the abdominal lymphatics and its numerous aetiologies include abdominal surgery, malignant neoplasms, blunt abdominal trauma, spontaneous bacterial peritonitis, cirrhosis, pelvic irradiation, peritoneal dialysis, abdominal tuberculosis and congenital defects in lacteal formation (Ablan *et al.*, 1990). In genitourinary oncological surgery, chylous ascites has been reported as a complication of retroperitoneal lymphadenectomy for testis cancer and regional lymphadenectomy for renal or adrenal tumours. The tumour burden and administration of adjuvant oncological therapy do not influence its development (Ferrigni and Novicki, 1985). The most common surgical cause is resection of abdominal aortic aneurysm. Diagnosis of the condition is based on paracentesis, which excludes other causes of ascites and demonstrates high concentrations of both fat and total protein in the ascitic fluid. The mainstay of treatment is dietary manipulation. Long-chain triglycerides are absorbed in the intestine and pass along omental lymphatics to the cisterna chyli and then to the thoracic duct. Medium-chain triglycerides are absorbed directly into the portal venous system, bypassing the lymph system and reducing the amount and flow of chyle. We suggest that such patients are commenced on a low fat medium-chain triglyceride diet as soon as the diagnosis is made. If this regimen fails or if the patient becomes increasingly cachectic, total parenteral nutrition should be used. Peritoneovenous (LeVeen) shunting carries appreciable morbidity and should be reserved for patients who do not respond to conservative measures.

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Combined Scleroidal and Choroidal Metastasis from Prostatic Carcinoma

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The skeleton and lymph nodes are well known sites of metastatic deposits from primary prostatic carcinoma. We report a patient with ocular metastasis from this tumour presenting with deterioration of vision in one eye.

Case Report

A 69-year-old man with a 4-year history of prostatic carcinoma developed disseminated disease with bony metastases (T4NXM1) and was treated by bilateral orchiectomy and flutamide anti-androgen hormone therapy. He subsequently presented with deterioration of vision in his left eye. Clinical examination revealed slight exophthalmos of the left eye and fundoscopy showed nasal and inferior retinal detachment secondary to a choroid mass. Visual acuity was 3/36 on the left and 6/6 on the right. Ultrasound scan of the left orbit confirmed extensive retinal detachment from a solid mass of the choroid in association with a posterior scleroid lesion 1 cm in diameter (Fig. 1). Serum prostatic specific antigen and alkaline phosphatase were markedly elevated at 74 μg/l and 337 u/l respectively. Excision biopsy of the scleroidal nodule showed an undifferentiated adenocarcinoma which was positively stained immunocytochemically (Steffens *et al.*, 1985) for both prostatic specific antigen and prostatic acid phosphatase, indicating a tumour of prostatic origin (Fig. 2). He was subsequently treated by a combination of radiotherapy to the left orbit and intravenous strontium micro-radiotherapy for the symptomatic bony metastases.

Comment

Common sites of metastases from prostatic carcimona include the skeleton, the lymphatic system, the liver and the lungs (Samsonov, 1985). Orbital or ocular metastases (Harnett *et al.*, 1987) are rare and scleroidal metastasis has not previously been documented. Like the cornea, the sclera is a relatively avascular part of the eye and hence blood-borne secondary deposits are uncommon.

Our patient developed progression of his prostatic carcinoma despite hormone therapy and hence his prognosis is poor. The deterioration of vision was caused by retinal detachment secondary to the choroidal metastasis. The scleroid nodule probably originated from the vascular choroid in view of their close proximity to each other. He was treated with palliative radiotherapy for his eye with the aim of preventing further deterioration of vision. In the presence of other metastases, enucleation is unnecessarily mutilating.

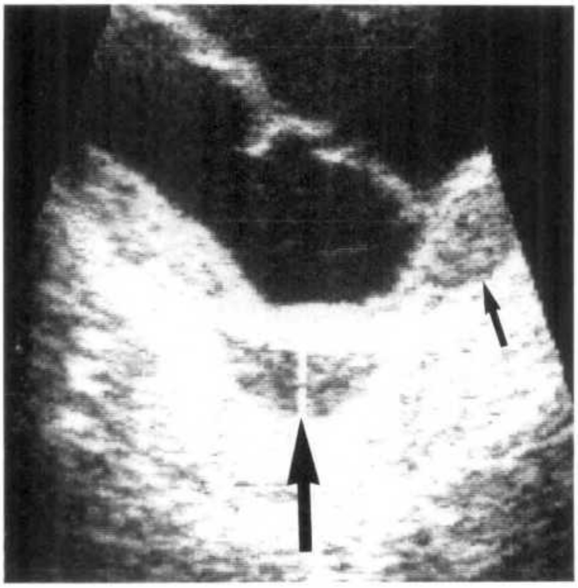

Fig. 1 Ultrasound scan of the orbit showing extensive retinal detachment and tumour masses of the choroid (small arrow) and sclera (large arrow) posteriorly.

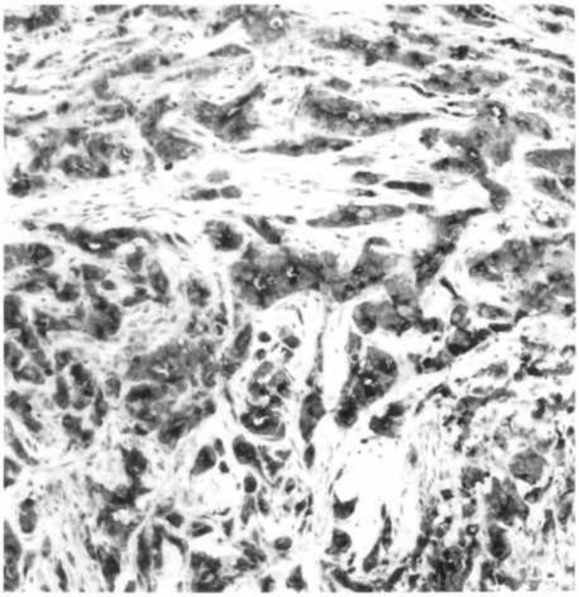

Fig. 2 Biopsy from the scleroid nodule (×250) showing an undifferentiated tumour with positive immunocytochemical staining (dark stain) for prostatic specific antigen.

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Extracorporeal Shock Wave Lithotripsy in Renal Transplant Patients

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Two cases of treatment by extracorporeal shock wave lithotripsy (ESWL) with the Siemens Lithostar Lithotriptor using electromagnetic shock wave generation and biplanar X-ray localisation are reported.

Case Reports

Case 1. A 40-year-old lady presented with recurrent urinary tract infections in a transplanted kidney. Investigations revealed multiple renal calculi and partial obstruction. Renal function was impaired and a percutaneous nephrostomy was inserted.

Four courses of ESWL, totalling 8900 shocks, were given at 18.4 kV.

Clearance of fragments was prevented by a ureteric stricture revealed by a nephrostogram. At follow-up the patient remains asymptomatic with normal renal function despite retained fragments.

Case 2. A 38-year-old lady presented with rigors following recurrent urinary tract infections. IVU showed a 1 × 2 cm stone impacted in the pelviureteric junction producing hydronephrosis (Fig.).

Three courses of ESWL, totalling 17,773 shocks, were given at 19.0 kV.

After complete fragmentation, a subsequent IVU was normal with no residual calculus.

Both patients experienced minimal discomfort during treatment and renal function returned to normal.

Comment

Calculus formation occurs in less than 1% of all transplanted kidneys (Locke *et al.*, 1988). Predisposing factors include secondary hyperparathyroidism, renal tubular acidosis, papillary necrosis, hypercalciuria, hyperoxaluria and recurrent infections. Treatment of these calculi may be by surgery, percutaneous nephrolithotomy or by ESWL (Kulb *et al.*, 1986).

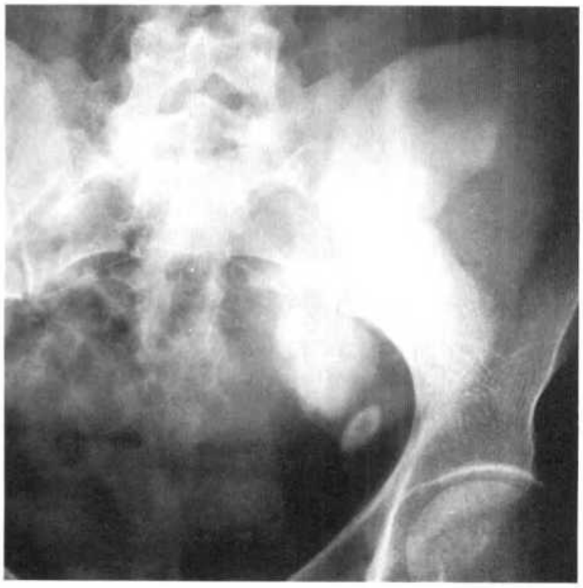

Fig.

The Lithostar allows treatment of calculi throughout the upper urinary tract. Using fluoroscopic imaging, accurate focusing of the shock waves is achieved by treating these patients prone. These factors enable treatment of calculi in the transplanted kidney.

Lithotripsy is an effective method of treating calculi in a transplanted kidney (Ellis *et al.*, 1989). Patients experience minimal discomfort and there is no change in renal function of the graft. However, the potential hazard of obstruction of a solitary functioning kidney (Kulb *et al.*, 1986), together with immunosuppression, must be considered. The transplant patient represents a higher risk and requires close monitoring after ESWL.

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"Interstitial Ureteritis": A Rare Cause of Bilateral Hydronephrosis

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The histological features of interstitial cystitis in the bladder have been well documented (Holm-Bentzen and Lose, 1987) but the possible changes in the rest of the urinary tract have not been described. We describe a case in which direct involvement of the ureters by the interstitial cystitis disease process resulted in bilateral hydronephrosis.

Case Report

A 66-year-old man presented with a 3-month history of frequency, urgency, nocturia and suprapubic discomfort. His serum creatinine and urea levels were normal and an IVU showed normal upper tracts. At cystoscopy, the typical appearances of interstitial cystitis were seen and a bladder biopsy confirmed the diagnosis of interstitial cystitis. He failed to respond to a Helmstein's bladder distension, but his symptoms were improved by oral steroids.

Eighteen months after presentation, he was found to have an elevated serum creatinine (216 μmol/l) and urea (26 mmol/l). An IVU showed bilateral hydronephrosis and a small residual volume (Fig. 1). Cystoscopy was performed to exclude carcinoma *in situ* and he proceeded to a laparotomy. At the operation, the lower end of the ureters appeared to be involved in an inflammatory process and the possibility of retroperitoneal fibrosis was entertained. The lower thirds of the ureters were excised and urinary diversion performed.

The histological sections of the ureters showed mucosal oedema and transmural, patchy chronic inflammation of the ureter, with fibrosis of the peri-ureteric tissues (Fig. 2A). Toluidine blue staining demonstrated frequent scattered mast cells mainly within the ureteric smooth muscle (Fig. 2B). Overall, the appearances mirrored those of previous bladder biopsies.

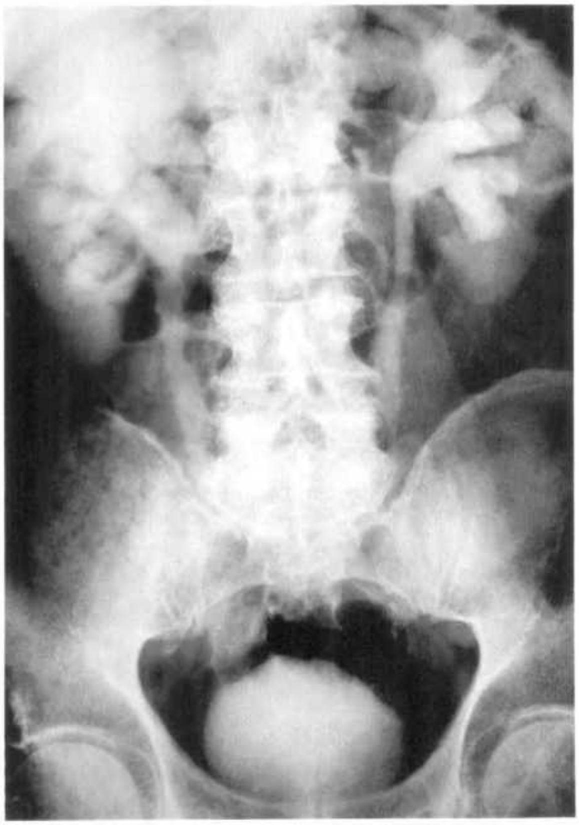

Fig. 1 IVU demonstrating bilateral hydronephrosis.

Comment

Bilateral hydronephrosis is frequently associated with systemic lupus erythematosus cystitis (Weisman *et al.*, 1981; Vicencio *et al.*, 1989) and it has

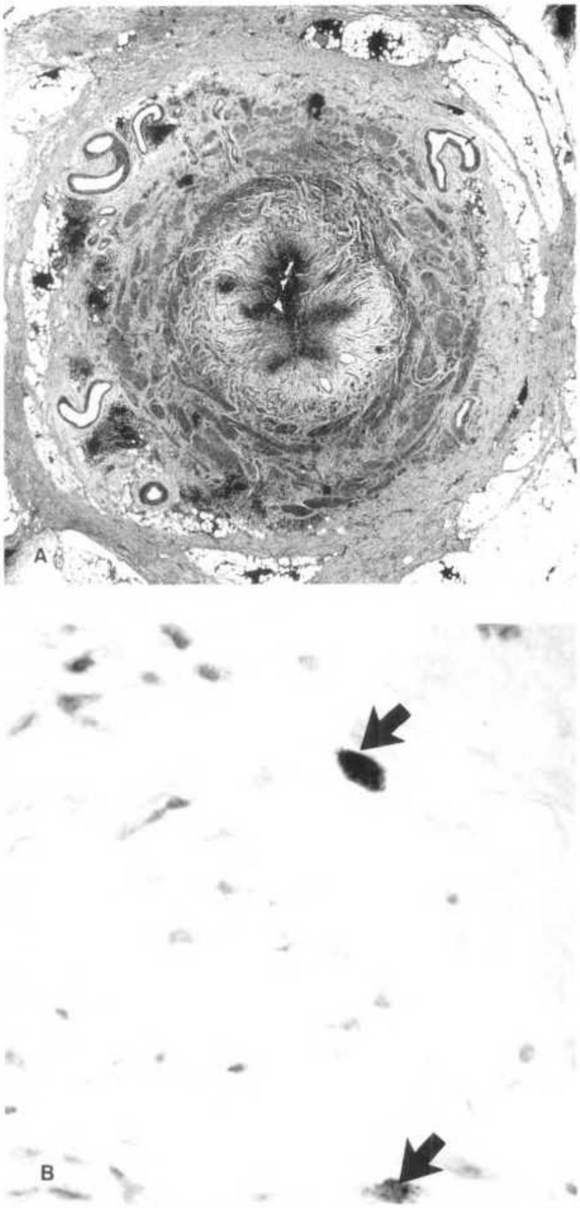

Fig. 2 (A) Cross section of the ureter (H and E ×10). (B) Interstitial mast cells (→). (Toluidine blue × 360).

been attributed to the high intravesical pressure, resulting in vesicoureteric reflux. Although it has also been reported in a case of eosinophilic cystitis (Horowitz *et al.*, 1972), there has been no previous report of hydronephrosis occurring in chronic interstitial cystitis or of ureteric involvement by the disease.

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Thirty-year Follow-up of Lymphogranuloma Venereum

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Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis* and accounts for 2 to 6% of all sexually transmitted diseases worldwide. Changes affecting the bladder have rarely been described.

Case Report

A 59-year-old West Indian complained of frequency and urgency of micturition precipitated by alcohol. The episodes were rapidly curtailed by tetracycline. Thirty years previously he had contracted lymphogranuloma venereum and had been treated with several courses of antibiotics.

On examination he appeared well and was apyrexial. The right groin was scarred and the right side of the pelvis felt indurated on rectal examination. The external genitalia were normal.

Examination of a mid-stream specimen of urine revealed a sterile pyuria. Haemoglobin, urea, electrolytes and ESR were all normal. An intravenous urogram revealed asymmetrical compression of the bladder (Fig. 1), thought to be due to extrinsic compression by scarred lymph nodes. A CT scan revealed a grossly thickened and apparently contracted bladder suggestive of malignancy (Fig. 2). There was no significant lymphadenopathy. Pre- and post-micturition bladder volumes measured by ultrasound were 800 and 100 ml respectively.

At cystoscopy there was a 2 cm white encrusted area just inside the bladder neck which was biopsied. The bladder was thickened, indurated and immobile on

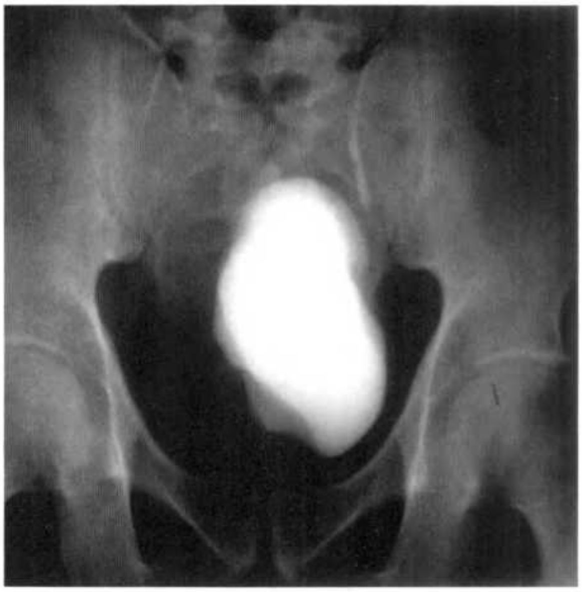

Fig. 1 Intravenous urogram showing a deformed bladder. (Upper urinary tracts were normal).

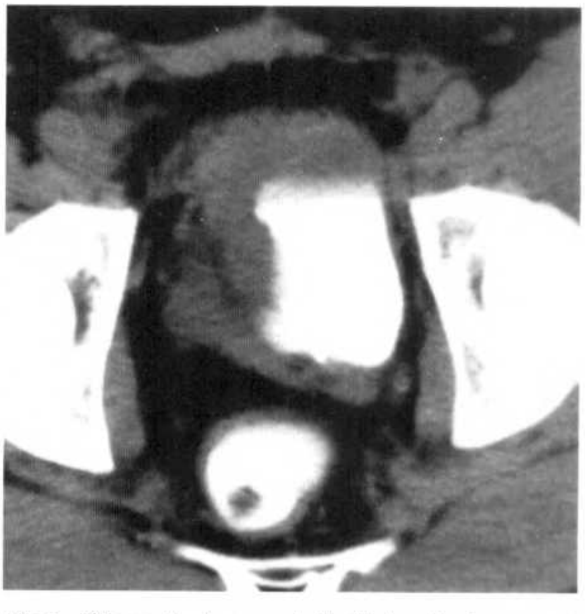

Fig. 2 CT scan showing a markedly thickened and apparently shrunken bladder. Some enlarged lymph nodes are present in the right internal iliac group.

bimanual palpation. Histology revealed squamous metaplasia with hyperkeratosis. In areas of transitional mucosa there was oedema, congestion and chronic inflammation. He has remained asymptomatic for the past 3 years.

Comment

The clinical course of LGV may be divided into 3 stages (Schachter and Osoba, 1983). The initial incubation stage ranges from 3 to 30 days before a small painless ulcer or papule appears on the penis or cervix. The second stage in men occurs at 2 to 6 weeks with unilateral lymphadenopathy which is often painful and tends to ulcerate. Groin lymphadenopathy may persist and spread, causing complications such as rectal strictures, proctitis and, in women, recto-vaginal fistulae (genito-ano-rectal syndrome or tertiary stage). Gross scrotal and penile oedema (elephantiasis) may also develop. Treatment in the early stages with oxytetracycline or sulphadiazine is more likely to be effective than when a chronic stage has been reached (Schachter and Osoba, 1983).

In our patient chronic infection caused initial retroperitoneal lymph node enlargement and involvement of the bladder. It is possible that alcohol reactivated inflammation in the bladder wall. The response to tetracycline and the presence of a sterile pyuria suggest reactivation of low grade LGV infection.

Reference

Schachter, J. and Osoba, A. O. (1983). Lymphogranuloma venereum. *Br Med. J.*, **39**, 151–154.

Requests for reprints to: N D. Heaton, Firm II Office, Department of Urology, King's College Hospital, Denmark Hill, London SE5 8RX.

Primary Carcinoid Tumour of the Spermatic Cord

J. R. McGREGOR, E. A RAWEILY, D. R. McLELLAN and A. G. HUTCHISON, *Departments of Urology and Pathology, Victoria Infirmary, Glasgow*

Case Report

A 50-year-old healthy man presented with a 2-cm irregular mass in the upper pole of the right testis. Surgical exploration revealed a yellow/grey neoplastic lesion arising from the distal spermatic cord and orchiectomy was performed. The tumour comprised rests of uniform polygonal cells with no evidence of mitotic activity or nuclear pleomorphism, but it exhibited positive staining with argentaffin and argyrophil reagents. Electron microscopy confirmed an abundance of neurosecretory granules. Microscopically the testis was normal.

Abdominal ultrasound and radiological examination of the gastro-intestinal tract showed no abnormality. The patient remains asymptomatic with undetectable urinary 5-hydroxy-indole acetic acid (5-HIAA) levels 18 months after surgery.

Comment

Only 2 cases of carcinoid tumour of the spermatic cord have been reported, 1 of which was considered to be metastatic from an extra-gonadal primary (Berdjis and Mostofi, 1977). Carcinoid tumours of the testis are also rare, accounting for less than 0.5% of all testicular neoplasms. Primary lesions usually present as painless progressive unilateral testicular enlargement with a peak incidence at 40 to 60 years (Talerman *et al.*, 1978). The history tends to be longer than for germ cell tumours and there is no predilection for maldescended or undescended gonads. The carcinoid syndrome is uncommon, although metastatic spread from an apparently primary testicular carcinoid has been recorded (Talerman *et al.*, 1978). Urinary 5-HIAA has only once been found to be elevated prior to orchiectomy (Nichols *et al.*, 1985) but post-operative serial estimation is essential in follow-up.

In contrast to the poor outlook associated with carcinoid tumours metastatic to the testis, the prognosis following inguinal orchiectomy for primary testicular carcinoid is excellent. However, the importance of long-term follow-up cannot be overemphasised, bearing in mind the possibility of delayed metastases and of multicentricity.

References

Berdjis, C. C. and Mostofi, F. K. (1977) Carcinoid tumours of the testis. *J. Urol.*, **118**, 777–782.

Nichols, D. A., James, E. M., Carboneau, J. W. ***et al.*** (1985). Imaging of a primary carcinoid tumour of the testis. *J Ultrasound Med.*, **4**, 225–226.

Talerman, A., Gratama, S., Mirnada, S. ***et al.*** (1978). Primary carcinoid tumor of the testis; case report, ultrastructure and review of the literature. *Cancer*, **42**, 2696–2705

Requests for reprints to: J. R. McGregor, Department of Surgery, Western Infirmary, Glasgow G11 6NT.

British Journal of Urology (1992), 70, 695–698

Correspondence

Dear Sir,

re **Erosion of buttress following bladder neck suspension.** R. E. Weiss and E. Cohen. *Br. J. Urol.*, **69**, 656–657, 1992.

I was interested to read this Case Report of erosion of the buttress related to a Stamey endoscopic bladder neck suspension procedure. I have now performed a little over 200 of these procedures and I have had to remove a buttress together with some nylon suture from the bladder on 3 occasions following my own surgery (and on one occasion following this procedure performed at another hospital). This would suggest that the incidence of this complication is approximately 1.5%.

I think this complication should be drawn to the attention of surgeons involved in the treatment of genuine stress incontinence for 2 reasons. First, it is not yet a well recognised complication and hence there may be considerable delay in making the diagnosis when symptoms occur that are compatible with this complication. I suspect that had Drs Weiss and Cohen considered this complication in their patient, they would have performed a cystoscopy rather than an intravenous urogram in the first instance. Second, in this climate of increasing claims for medical negligence, I believe that doctors who give opinions should be aware that this complication relates to migration of material through the bladder wall and not to misplacement of suture and buttress at the time of initial surgery.

It will now become important to document whether my estimate of 1.5% for the incidence of this complication is accurate or whether other surgeons involved in the management of genuine stress incontinence can produce other statistics.

Yours faithfully,

G. J. Jarvis
Urogynaecology Department, St James's University Hospital, Leeds

Dear Sir,

re **Acute urinary retention caused by anterior urethral polyp.** N. Anandan *et al. Br. J. Urol.*, **69**, 321–322, 1992.

The above authors reported a new case of urethral polyp and commented on the probable congenital origin of this lesion.

We have recently treated a 51-year-old male with a polyp in the posterior urethra causing acute urinary retention. Three months previously he had presented with dysuria and a gradually worsening stream. Urethral catheterisation was impossible, so we performed temporary suprapubic cystotomy. Cystourethroscopy revealed a polyp occupying the prostatic urethra which was resected transurethrally. Histology disclosed a benign polyp which was lined by 3 to 4 layers of well differentiated transitional cells with fibromuscular stroma without convincing evidence of invasion of submucosal tissue. Six months post-operatively he is absolutely normal.

Although we cannot exclude its congenital nature, we note the patient's age, the short history and the lack of haematuria, which seems to be the commonest symptom (Downs, R. A. *Br. J. Urol.*, **42**, 76–85, 1970).

Yours faithfully,

P. Perimenis and A. Panagou
Department of Urology, University of Patras, Patras, Greece

Dear Sir,

re **Routine radio-imaging in filarial chyluria—is it necessary in developing countries?** D. Dalela *et al. Br. J. Urol.*, **69**, 291–293, 1992.

I agree with the authors of the above article that routine retrograde pyelography and lymphangiography are not essential in the management of filarial chyluria. However, I do not agree with some aspects of treatment.

Four renal pelvic instillations of silver nitrate at weekly intervals, as practised at institution A, are adequate and safe. However, the administration of 3 silver nitrate instillations per day for 2 or 3 days, as practised at institution B, may cause permanent renal damage. Over-instillation of silver nitrate can cause anuria in solitary kidneys and is potentially harmful, so great caution should be exercised.

Renal pelvic instillations of 1% silver nitrate also cause severe pain and should therefore be administered only to in-patients.

Yours faithfully,

A. Basu
Department of Surgery, North Devon District Hospital, Barnstaple.

Dear Sir,

Method of dealing with huge bladder stones

Occasionally, bladder stones large enough to require open cystolithotomy may prove difficult to remove at operation. We recently encountered this problem, to which there is a simple solution. A 63-year-old lady with a history of neurosyphilis, epilepsy and traumatic quadriplegia was referred with persistent incontinence of urine, despite the presence of a long-term indwelling urethral catheter. Investigation revealed a bladder calculus 12 cm in diameter. At operation a suprapubic cystotomy was made, but it proved impossible to introduce a finger into her bladder. The stone completely filled the bladder and could not be moved upwards by pressure applied to the anterior wall of the vagina. Fortunately, the difficulty had been anticipated and a pair of sterile Wrigley's obstetric forceps were available. Delivery of the stone was effected with ease.

The chief advantages of this technique are the speed and ease with which the calculus can be removed, causing minimum trauma to the bladder. Other possible approaches to the problem could include a prior or per-operative attempt at lithotripsy (Bosco, P. J. and Nieh, P. T. *J. Urol.*, **145**, 34–36, 1991) or significant extension of the cystotomy, and these compare unfavourably with the use of obstetric forceps in this situation (Jeffrey, *Urology*, **21**, 162–3, 1983). The size and shape of the Wrigley's forceps are ideally suited to the task. Such difficulty needs to be anticipated, however, so that the equipment can be sterilised and available.

Yours faithfully,

D. Lanigan and R. G. Choa
Department of Urology, Derriford Hospital, Plymouth

Dear Sir,

re **Transrectal ultrasound 1992.** D. Rickards. *Br. J. Urol.*, **69**, 449–455, 1992.

Whilst enjoying this Review article, I would take issue with the author's statement "There are no significant complications", referring to transrectal needle biopsy. Rickards subsequently recommends the use of prophylactic antibiotics and a cleansing enema, with which most practitioners of the technique, I believe, would agree.

First, serious traumatic and infective complications (prostatic abscess, urinary tract infection, septicaemia) are well documented and occasionally fatal. Second, the questions of how and when to administer which antibiotic(s) are unanswered at present. Earlier this year I sent a questionnaire addressing this subject to 25 centres in the UK; 19 replies were received. None of the respondents routinely applies a local antiseptic prior to biopsy. All routinely prescribe some form of antimicrobial prophylaxis, ranging in complexity from a single oral dose of ciprofloxacin 250 mg 20 minutes prior to biopsy to an elaborate regimen consisting of gentamicin 120 mg intravenously and metronidazole 1 g rectally prior to biopsy, followed by cephalexin 500 mg *b.d.* for 5 days. None of the responses was the same.

The benefit in terms of reducing infective complications by application of a cleansing enema to the anterior rectal wall prior to biopsy is proven (Melekos, M. D. *Int. Urol. Nephrol.*, **22**, 257–262, 1990). Appropriate single-agent, single-dose intravenous antimicrobial prophylaxis should rapidly achieve good tissue levels and adequately cover relevant pathogens without dependence on patient compliance. This is the subject of a current prospective study in this department.

Yours faithfully,

S. F. Brewster
Department of Urology, Southmead Hospital, Bristol

Dear Sir,

re **Perineal ectopic testis.** H. Dogruyol and E. Balkan. *Br. J. Urol.*, **69**, 547, 1992.

Perineal ectopic testis is a very uncommon occurrence, as borne out by the few series cited by the authors. Recently, we have seen 2 more cases. In addition, we would like to raise a basic issue—photographic illustration of physical findings not immediately apparent. In the figure accompanying the article, the otherwise invisible ectopic testis is seen grasped between the finger and thumb of the clinician. The photograph was evidently taken from the bed-end with the baby lying supine. The reader might be under the impression that the testis is in the femoral region, which is another well known

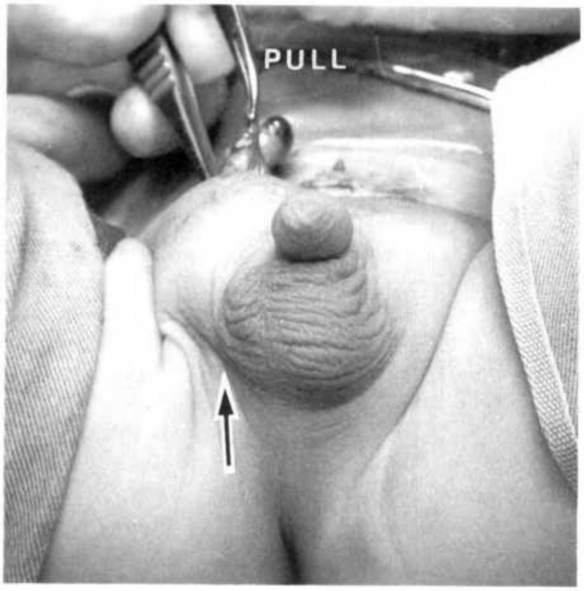

Fig. 1

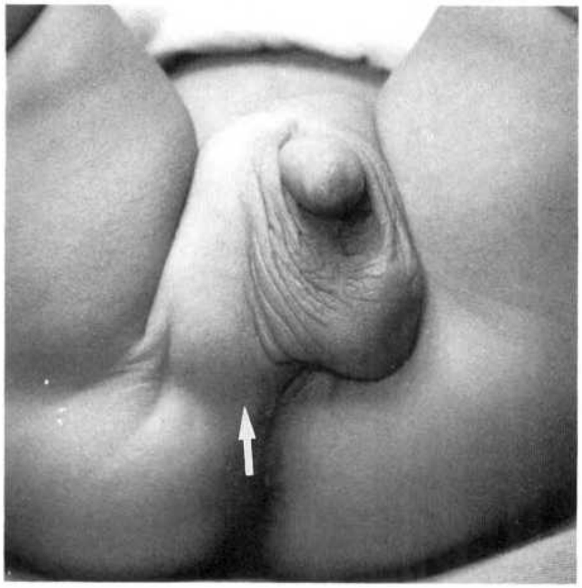

Fig. 2

and more common location for ectopic testes (Middleton G. W. *et al. J. Urol.*, **115**, 455–458, 1976). Possibly the testis has been displaced to some extent to the anteromedial aspect of the upper thigh by the examiner's hand.

By definition, perineal ectopic testis is a testis lying fixed between the scrotum and the anus. We suggest the photographic demonstration of this condition be illustrated as in Figs 1 and 2. Since the affected testis is tethered by a solitary fibrous gubernacular cord to the overlying dermis, at operation, traction on the testis would result in an observable dimple (arrow) indicating its perineal origin (Fig. 1). A perineal testis is not apparent when the photograph is taken with the baby lying supine and lower limbs extended, but drawing up the thighs forcefully renders it visible as a localised bulge (Fig. 2).

Yours faithfully,

W. T. Ng, M. K. Wong, C. K. Kong and Y. T. Chan
Department of Surgery, Princess Margaret Hospital, Lai King, Hong Kong

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Dear Sir,

re **Cystodiathermy under local anaesthesia using the flexible cystoscope.** K. German *et al. Br. J. Urol.*, **69**, 518–520, 1992.

The fulguration of bladder tumours by diathermy and laser using urethral local anaesthesia is associated with considerable discomfort to the patient, especially in the trigonal region. This is liable to result in suboptimal local treatment of any but the smallest tumour.

We have found that the direct infiltration of lignocaine and adrenaline (1 in 200,000. 15–20 ml) not only provides complete local anaesthesia and good resecting conditions but obviates obturator nerve responses. Extensive tumour resection (4–5 cm) can proceed with ease. We now have substantial experience of local anaesthetic bladder surveillance, cystodiathermy and tumour resection and have performed over 400 fulgurations and 170 transurethral resections of bladder tumours using sedoanalgesia. In our opinion the combination of topical anaesthesia and low levels of sedation provides a more satisfactory environment for the patient and surgeon alike.

Yours faithfully,

K. M. Anson, P. Shridhar, G. M. Watson and R. A. Miller
Department of Urology and Minimally Invasive Surgery, The Whittington and Royal Northern Hospitals, London

Reply from Messrs German, Hasan and Derry. The purpose of our article was to show that when the flexible cystoscope is used for bladder tumour surveillance, the fulguration of *small* recurrence is effective and well tolerated using only topical urethral anaesthesia. The technique is simple, quick and cheap (the cost of a diathermy electrode) and makes use of the pre-existing diathermy equipment. We found that fulguration of recurrences on the trigone and bladder neck was painful and recommended infiltration with local anaesthetic if one was intending to proceed with fulguration at these sites.

Although we agree that local anaesthetic infiltration and sedoanalgesia may enable the resection of larger recurrences (using a rigid cystoscope), it was our policy to readmit these patients for their procedure under general/regional anaesthesia.

Dear Sir,

re **Harpoon device for removal of obstructed balloon catheters.** K. J. O'Flynn *et al. Br. J. Urol.*, **69**, 217–219, 1992.

The authors have described an interesting technique to deflate obstructed balloon catheters. The technique may be applicable in patients with no urethral sensation (*e.g.* spinal cord injury) but I cannot imagine how one could achieve adequate local anaesthesia of the urethra sufficient to permit the passage of a cystoscope sheath with a catheter already present.

There have been a few publications describing how to tackle an obstructed balloon catheter, including this suggestion by Mr O'Flynn and colleagues and the other by Saxena and colleagues in the same issue of the British Journal of Urology. However, there are no published data examining why Foley catheter balloons should fail to deflate in the first place.

Many surgeons are guilty of using any form of liquid which resembles water to inflate the balloon. The most common is the fluid from the hand-rinsing bowl; this often contains small particles, including blood clots, which can easily cause obstruction to the fine balloon channel of the catheter. If this practice were to stop, the incidence of obstructive balloon catheters would drop.

Yours faithfully,

S. Shroff
Institute of Urology and Nephrology, London.

British Journal of Urology (1992), **70**, 699–700

Notices

British Association of Urological Surgeons

President: J. C. Smith, MS, FRCS

Annual Meeting: Harrogate, 22–25 June 1993

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1992. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 8th January 1993.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

Institute of Urology and Nephrology (University College London) in association with St Peter's Hospital

Preliminary Academic Programme 1992/1993

11 December 1992
Urolithorama

11–22 January 1993
Short Courses in Urology and Nephrology (including Urological Cancers; Upper Tract Obstruction; Stone Disease; Prostatic Disease; Trauma)

11 February 1993
Uro-radiology

February 1993
Advances in Minimally Invasive Surgery

15–18 March 1993
Uro-andrology

19–20 March 1993
International Symposium of Operative Andrology

March 1993
New Techniques in Prostatic Outflow Obstruction

April 1993
Urology for the FRCS

19 April–7 May 1993
Short Courses in Urology and Nephrology (including Female Urology; Reconstructive Surgery; Paediatric Urology; The Elderly; Tropical Diseases; Urology of the Future)

For further information please contact: The Course Secretary, Institute of Urology and Nephrology, 48 Riding House Street, London W1P 7PN. Tel: 071 380 9381/9372.

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £1000 to the author of the article(s) judged to be the most outstanding each year (2 volumes) in the British Journal of Urology. Candidates for the prize must be Fellows of the Royal College of Surgeons in the British Isles, Canada, Australia or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prizewinner must submit a programme of visits to urological centres outside Britain. This prize is not necessarily awarded annually.

British Journal of Urology Travelling Fellowship

This fellowship of £1500 enables a Senior Registrar or numbered Career/Research Registrar to attend the American Urological Association Meeting. It is awarded in April each year at the Annual Scientific Meeting of the Senior Urological Registrars Group (SURG). The award is given for the better of two papers presented at this meeting on a vote by the members of SURG present at the meeting. Invitations to the meeting are sent out in January by the Chairman of the Senior Urological Registrars Group and papers must be new work not previously published and not resulting from a thesis.

Lewis Medical Travelling Scholarship

The scholarship covers travel, accommodation and registration expenses associated with attending the Annual Meeting of the American Urological Association. The scholarship will be available to any person appointed to a numbered urological training post and will be awarded to the person presenting the winning paper at the Annual Meeting of the Senior Urological Registrars Group. An additional scholarship may be awarded at the discretion of the Senior Urological Registrars Group and Lewis Medical Limited.

Simpla Research Prize

Simpla Plastics Limited offer an annual prize of £1500 to support a basic clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be sent to the Honorary Secretary by 1 April. The prize will be awarded at the Annual General Meeting.

Urological Research Society

The first meeting of the Urological Research Society (formerly the Guy's Annual Research Meeting) will take place at Guy's Hospital, London, on Friday, 8 January 1993. Further information about attendance and the presentation of papers from Professor A. R. Mundy, Academic Department of Urology, Guy's Hospital, St Thomas' Street, London SE1 9RT. Tel: 071-955 4659. Fax: 071-955 4675.

Prizes and Awards

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

At the 48th Annual Meeting of BAUS held in the Bournemouth International Centre, Bournemouth on 23–26 June 1992, the following awards were made:

St Paul's Medal

At the Annual Dinner the President presented the St Paul's Medal to Professor M. Ghoneim after a citation given by Professor J. Mitchell.

BAUS Travelling Fellowship

No award was given for 1992.

Surgitek Prize

The 1992 Surgitek Prize was awarded to Mr J. A. Vale for his paper entitled "The late irradiation injury of the urinary bladder".

Simpla Research Prize

The 1992 Prize was awarded to Mr A. Doble and Mr L. Trejdosiewicz for their project entitled "The metastatic potential of adenocarcinoma of the prostate: the role of cell adhesion molecules".

Bard Award

The prize and Bard Silver Medal for 1992 were given to Miss Anne M. Jequier for her essay entitled "The impact of reproductive technology on the management of infertility in the male".

William Cook Travelling Fellowships

Fellowships were awarded to Messrs P. Duffy and S. Liu.

Lewis Medical Travelling Scholarship

The scholarship was awarded to Mr P. Britton

British Journal of Urology Travelling Fellowship

The fellowship was awarded to Mr R. Webb

1992 Shackman Travelling Fellowships

Fellowships were awarded to Mr I. Eardley, Mr T. Christmas and Mr R. C. Kockelbergh.

British Journal of Urology (1992), 70, 701–702

Diary

1992

December 4–5	Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.

1993

January 26–29	Ninth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev, Denmark. Contact: Dr F. Rasmussen, Department of Urology, Herlev Hospital, DK-2730 Herlev, Denmark.
March 14–15	State-of-the-Art Genitourinary Ultrasound Course. Honolulu, Hawaii. Contact: American Institute of Ultrasound in Medicine, Convention Department, 11200 Rockville Pike, Suite 205, Rockville, Maryland 20852, USA. Tel: (301) 881-2486. Fax: (301) 881-7303
March 19–20	Second European Congress on Ambulatory Surgery. Brussels, Belgium. Contact: Dr C. De Lathouwer, Brussels One Day Clinic, Avenue du Duc Jean 71–73, B-1080 Brussels, Belgium. Tel: +322/424.1212. Fax: +322/425.7076.
March 27	First International Symposium on Bladder Cancer. "BCG immunotherapy in superficial bladder cancer. The 1993 state of the art". Padova, Italy. Contact: Professor F. Pagano, Department of Urology, University of Padova, Via Guistiniani 2, 35128 Padova, Italy. Tel: 049-8212720. Fax: 049:8212721.
April 19–22	2nd Interamerican Meeting on Pediatric Urology. Viña Del Mar, Chile. Contract: Dr Ricardo Gonzalez, 420 Delaware Street, S.E. Box 45, University of Minnesota Hospital, Minneapolis, Minnesota 55455, USA. Tel: 612 625-9117. Fax: 612 626-2458 *or* Dr Ricardo Zubieta, Esmeralda 678, 3 er Piso, Of. 303, Casilla 639, Santiago, Chile. Tel: 56-2-331. Fax: 56-2-391 085.
May 16–20	American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
June 4–5	Fifth International Meeting of Andrology. "Corporal Veno-occlusive Dysfunction: Diagnosis and Treatment". Rome, Italy. Contact: Dr Diego Pozza, Centro di Andrologia e di Chirurgia Andrologica, via Flaminia Nuova 280, 00191 Rome, Italy. Tel. and Fax: +39.6-3270741.
June 20–24	Canadian Urological Association Annual Meeting. Montreal, Canada. Contact: Dr Normand Sullivan, 1 Marianne, Sainte-Anne de Sorel, Quebec, Canada J3P 2Z4. Fax: (514) 743-1896.
September 26–30	International Symposium on Sex Hormones and Anti-hormones in Endocrine-dependent Pathology: Basic and Clinical Aspects. Milan, Italy. Contact: M. Motta or M. Serio, Department of Endocrinology, University of Milan, 9 Via Balzaretti, 20133 Milan, Italy. Tel. 02-20406576. Fax: 02-29404927.

November 4–6	Second International Congress of the Dutch Urological Association. "New Insights into the Aetiology, Diagnosis and Management of BPH". Amsterdam, The Netherlands. Contact: IMEDEX, P.O. Box 3283, 5203 DG 's-Hertogenbosch, The Netherlands. Tel: +3173429285. Fax: +3173414766.
1994	
May 15–19	American Urological Association, Moscone Centre, San Francisco, California.

Erratum

re **Clinicopathological Study of Nephroblastomas in Ibadan.** E. E. U. Akang, J. U. Okpala, Y. Iliyasu and J. Lawani.
Br. J. Urol. (1992) **70**, 318–321.

When this paper was published the surname of the last-named author, Mr J. Lawani, was omitted. This was an error on the part of the printers. We apologise for any inconvenience caused.

British Journal of Urology (1992), 70, 703–704

Book Reviews

Urological Prostheses, Appliances and Catheters (Clinical Practice in Urology Series). Edited by J. P. Pryor. Pp. xv + 288. London, Berlin, Heidelberg, New York, Paris, Tokyo, Hong Kong, Barcelona, Budapest: Springer-Verlag. 1992. Price: DM 235.00.

This book seeks to bring together the experience and expertise of a group of well known urologists in this rapidly expanding and changing field of urology. Herein lies the first problem. Because of the changes, this book could become out of date all too soon. The second problem is that most of the information is already available in standard urological texts. However, it is useful to collect the information in one volume and it will be of particular value to the trainee urologist when faced with using these appliances for the first time, and also to the experienced urologist when bringing his knowledge up to date or when faced with a problem patient.

It would perhaps have been simpler just to list the technical details of each appliance but the book also discusses in some detail the indications for each procedure. In some chapters the method of insertion of implantable devices is not as detailed as one might expect and the reader is referred to the relevant publication in an extensive bibliography. The complications are described together with the necessary remedial action.

Each part of the urological system is covered, starting with nephrostomy, ureteric stents, bladder catheters, implantable and external incontinence devices as well as urostomy appliances. Penile, vas deferens and testicular prostheses each merit a chapter, and the book ends with vascular access and antibiotic therapy, which describes the treatment of urinary tract infection as well as antibiotics in prosthetic surgery

The book is well edited and very readable, but one can always find something to criticise. There is a simpler way of deflating a Foley catheter than those described. The chapters on prosthetic urethral substitution and alloplastic spermatocele had to be included for the sake of completeness but are essentially experimental

A noteworthy feature is the emphasis on detailed explanation to the patient, which is essential for the acceptance and success of any operation.

Moving to Audit (What Every Doctor Needs to Know about Medical Audit). Developed and produced in the Centre for Medical Education, Ninewells Hospital and Medical School, Dundee. Pp. viii + 128. 1992. Price: £12.50 (+£1.50 p.p.).

Good medical audit has been around for a long time now and the enthusiasts have welcomed recent initiatives by the Government if only because the money is good and they find themselves resourced as never before. Understandably this has led to some cynicism from honest doubters and the disinclined to an extent that the substantial benefits to good practice that may accrue from audit become obscured. Such attitudes are further encouraged by a profusion of indifferent audit that medical audit committees have to try to knock into shape.

This book, which comprises an educational package for hospital doctors and general practitioners from the University of Dundee, is a breath of fresh air. The package consists of a resource book and a series of audit challenges and projects. This allows the doctor to find his way through the interactive learning course at his own pace and personalised feedback is available.

It is primarily aimed at the beginner, but there is much of interest for the more experienced medical auditor. It is very easy to read but only lightly referenced. The style and layout are interrogative but stimulating, with points to ponder highlighted and lessons learned reinforced. Although it is aimed at disparate groups of doctors, the widespread use of examples helps to emphasise principles of methodology and the presentation is effective.

There will always be many examples of poor and ineffective audit. Those about to embark on any project would be well advised to read this inexpensive resource book at £12.50 or take the whole course at £29.00 before they start.

Radiology of Organ Transplantation. Edited by Janis G. Letourneau, Deborah L. Day and Nancy L. Ascher. Pp. xvi + 359. St Louis, Baltimore, Boston, Chicago, London, Philadelphia, Sydney, Toronto: Mosby Year Book. 1991. Price: £77.00.

Solid organ transplantation has made such great advances in the past 30+ years that it is no surprise that a special volume such as this has been produced. There are 5 parts: general radiological considerations, then the radiology of renal, hepatic, pancreatic and heart (lung) transplantation. Perhaps the title of the book is misleading because in each section all forms of imaging (scintigraphy, sonography, CT, MRI and angiography) are covered. This reviewer could comment only on the renal section, which gives a readable, comprehensive, up-to-date review of the role of imaging for diagnosing and managing the various complications that can occur.

Current Operative Urology 1991. Edited by E. D. Whitehead. Pp. xxi + 426. Philadelphia, New York, St Louis, London, Sydney, Tokyo: Lippincott. 1991. Price: US $89.50.

This is the third of such books—the others appearing in 1975 and 1984. The format is unusual. Each subject is introduced by an important recent paper reproduced in full. This is followed by a commentary on that paper by an expert in the field and then an overview of the entire subject is given by another authority in that field. Each topic has an annotated bibliography. The book does not aim to be comprehensive and concentrates on new approaches and emerging developments in urological surgery. Nine topics have been selected with contributions varying from 3 per topic, as in the management of ureterocele, to 12 for the surgery of uretero-pelvic obstruction. This format proves very successful in bringing together a most authoritative picture of each topic. The plan is that there will be annual editions. A very useful reference source, especially for trainees.

International Nomenclature of Diseases. (Volume VII – Diseases of the Kidney, the Lower Urinary Tract, and the Male Genital System. Volume VIII – Diseases of the Female Genital System). Council for International Organizations of Medical Sciences, World Health Organization. Pp. xiii + 180 and xii + 126. Geneva: World Health Organization. 1992. Price: Volume VII Sw.fr. 20.-. US $18.00. Volume VIII Sw.fr. 23.-. US $20.70.

This is a comprehensive Nomenclature of Diseases with short descriptions to define the conditions (synonyms are given in brackets). The book is not a classification and there is no attempt to indicate frequent or infrequent conditions. This point is made in the Introduction. This nomenclature is not a substitute for ICD (International Classification of Diseases) but it is stated that IND names will be used in ICD 10 where appropriate and thus the IND should help where definitions are not clear. The nomenclature has been agreed by a panel of pathologists and many of the conditions are obscure and of minimal daily clinical relevance. Nevertheless, this will be a required reference for those concerned with definitions behind ICD 10 codes.

Book Received

Principles and Methods for the Assessment of Nephrotoxicity Associated with Exposure to Chemicals. Environmental Health Criteria, No. 119. (International Programme on Chemical Safety Commission of the European Communities). Pp. 266. Geneva: World Health Organization. 1991. Price: Sw.fr. 29.–. US$26.10.

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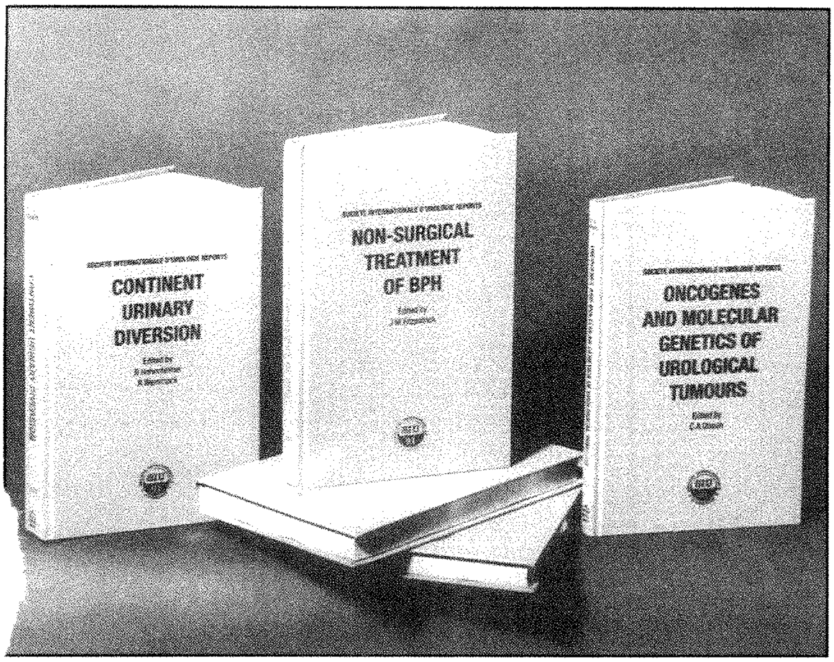
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